RETRIEVAL PROCESSES IN HEALTHY AGING, MILD COGNITIVE IMPAIRMENT, AND ALZHEIMER'S DISEASE

A Dissertation

Presented to the Faculty of the Graduate School

of Cornell University

In Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

by

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January 2017

RETRIEVAL PROCESSES IN HEALTHY AGING, MILD COGNITIVE IMPAIRMENT, AND AZLHEIMER'S DISEASE

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Cornell University 2017

Longitudinal changes in latent recall operations during healthy and unhealthy aging were investigated in two studies. In the first study, healthy younger adults and healthy older adults received neuropsychological exams and associative recall memory tests at three different occasions (waves A, B, and C), spanning a period of roughly 1 year and 6 months. In the second study, older adults diagnosed as healthy control (HC), mild cognitive impairment (MCI), or Alzheimer's disease (AD) had multiple clinical/cognitive assessments at specific intervals for a period of 3 years. In both studies, the recall data from each subject was analyzed with a Markov chain—the dual-retrieval model of recall—to extract measures of latent recollective recall (direct access) and reconstructive recall (reconstruction + familiarity judgment). The notion that normal age-related declines in episodic memory reflect changes in recollective retrieval was supported. In unhealthy aging, however, declines in reconstructive recall were the main marker of disease progression and the only operation able to differentiate HC subjects from MCI subjects, and MCI subjects from AD subjects. The reported findings suggest that unhealthy aging does not simply accelerate the

normal aging process because it affects memory processes that are often spared in healthy aging.

BIOGRAPHICAL SKETCH

Carlos Gomes is a graduate student in the Human Development department at Cornell University, United States. He has a bachelor's degree in Psychology from the Pontifical Catholic University of Rio Grande do Sul, Brazil, and Master of Arts degree in Human Development from Cornell University, United States. He has been involved with psychological research since his undergraduate education and has published journal articles and book chapters about memory research and related topics. As an undergraduate, he was awarded scholarships from the Brazilian National Council for Scientific and Technological Development for his work in false memory research and emotion. In 2012, he received a fellowship from the CAPES Foundation, a funding agency linked to the Brazilian Ministry of Education, to conduct research on the markers of impairment during aging. He is interested in three main areas of psychological research, namely memory development, particularly aging, modelling of retrieval processes, and false memories. Of late, his work has focused on two main lines of investigation. The first regards the investigation of retrieval processes that predict transitions between healthy and unhealthy aging, while the second focuses on the development of mathematical models and paradigms that identify different retrieval processes.

ACKNOWLEDGMENTS

I would like to thank my academic advisor and chairperson of my graduate committee, Dr. Brainerd, for his continuing guidance during the making of this dissertation and for all helpful commentaries on previous drafts. It has been both an honor and a pleasure to work with him for the last five years. I am also extremely thankful to the members of my graduate committee, Dr. Reyna and Dr. Wang, for taking time out of their busy schedule to talk about my dissertation and other academic work, and to the Cornell University and the Human Development department for supporting my research and for providing the facilities and materials. They have all provided direct contribution to the elaboration of my dissertation and made my academic plans possible.

I have met and worked with many people in the past who either directly or indirectly contributed to this dissertation. I offer my sincere and earnest gratitude to all of them, particularly to current and former members of the Memory and Neuroscience laboratory at Cornell who helped collecting and organizing much of the data reported in this dissertation. I am forever grateful to my first mentor in psychology, Dr. Stein, for instigating my curiosity and for providing invaluable advices throughout my undergraduate education. I thank all funding agencies who have sponsored me in the past, especially the Brazilian National Council for Scientific and Technological Development, for supporting research projects who gave me enough experience to conduct these and other studies, and to the members of all

research labs I have worked so far. Finally, I would like to thank both my parents for their unconditional love, for believing in me, and for supporting my decisions.

Preparation of this dissertation was supported by the CAPES Foundation, Brazilian Ministry of Education (BEX 0328/12-0).

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

In its chronological sense, aging is inevitable and universal to all—the ever continuing arrangement of events from past to present to future implies that anything and everything must age. In humans, aging is accompanied by remarkable physical, psychological, and social changes. Early in the developmental trajectory, for instance, a child will grow several times in size, will learn how to organize sets of symbols in order to communicate, and will create representations of experiences that will be the foundation of part of his or her personality. Later in life, wrinkles and grey hair are perhaps the most obvious physical changes, but cognition, too, is prone to change (Craik & Salthouse, 2011). Declines from early adulthood to old age in the ability to retrieve information from a particular event in the past (episodic memory) are one of the characteristic changes in cognition that occur later on in the developmental trajectory (Craik, 1994).

However, it is also later on in the developmental trajectory that the brain becomes particularly susceptible to age-related diseases of memory, such as Alzheimer's disease (AD) and its prodromal stage, mild cognitive impairment (MCI) (Hebert et al., 1995; Kukull et al., 2002; Plassman et al., 2007, 2008). Disentangling what is normal cognitive functioning from what is pathological is not always an easy task, especially in a discipline in which many phenomena under investigation (e.g., consciousness, representations) are often not directly observable. It is this latter aspect of aging that my dissertation is concerned with, namely how healthy and unhealthy aging affects memory later in life. More specifically, the main objective of the two

studies reported in this dissertation was to investigate the developmental trajectories of latent retrieval processes in healthy aging, MCI, and AD.

In what follows, I reported findings from two longitudinal studies. In the first study, healthy younger adults and healthy older adults received neuropsychological exams and associative recall memory tests at three different occasions (waves A, B, and C), spanning a period of roughly 1 year and 6 months. The recall data from each subject was analyzed with a Markov chain—the dual-retrieval model of recall (Brainerd, Reyna, & Howe, 2009; Gomes, Brainerd, & Stein, 2013; Gomes, Brainerd, Nakamura, & Reyna, 2014)—to extract measures of latent processes that control recall. Then, longitudinal patterns of change, as well as age group differences in retrieval processes, were modeled with a multilevel linear model (Laird & Ware, 1982). In the second study, older adults diagnosed as healthy control (HC), MCI, or AD had multiple clinical/cognitive assessments at specific intervals for a period of three years. As in the first study, latent retrieval process in recall were also measured with the dual-retrieval model and the data analyzed with a multilevel linear model. Contrary to the first study, however, the main interest in the second study was on process-level differences between healthy and unhealthy older adults.

Together, the studies provided a general picture of the developmental trajectories of retrieval processes during normal aging (Study 1) and abnormal aging (Study 2), which was contrasted with theoretical predictions and previous findings. As it would be expected, performance on recall tasks declined in healthy as well as unhealthy aging. However, not all declines in performance were equal—some were more closely connected to disease than others. This and other issues were discussed at

the end of the dissertation. In what follows, I reported background studies on Alzheimer's disease, mild cognitive impairment, and the effects of aging on memory.

Aging and Memory

Changes in cognition that occur with advancing age have been target of systematic investigation for several decades now (Craik & Salthouse, 2011). Over the years, such a literature has accumulated a plethora of age-related effects on cognition. One of such well-documented effects of normal aging is a generalized slowing down in mental operations (e.g., Verhaedhen & Salthouse, 1997) and a decline in numeric ability (Hedden & Gabrielli, 2004). For example, when younger and older adults are asked to perform a visual matching task, in which several sets of five numbers are presented during a limited period of time and subjects are asked to circle the two equal numbers within each set, older adults successfully complete fewer sets in the allotted time than younger adults (Salthouse, 1998).

Nonetheless, memory changes are one of the earliest age-related changes (Grady, 2008; Park & Gutchess, 2002). Performance on different memory tasks have also been well-documented (Craik, 1994) and importantly, such a literature has shown that while performance on some memory tasks decline, such as working memory (Verhaeghen, Marcoen, & Goossens, 1993), supra-span list recall (Petersen et al., 1992), and source memory (McIntyre & Craik, 1987; Spencer & Raz, 1995), performance on other tasks show little to no changes during normal aging, such as memory for concepts, general knowledge facts (Backman & Nilsson, 1996), fragment completion, and other implicit memory tasks (Fleischman & Gabrieli, 1998; La Voie & Light, 1994).

In Nilsson's (2003) study, healthy subjects from five different age groups—namely, 35-40 years, 45-50 years, 55-60 years, 65-70 years, and 75-80 years—received episodic memory tasks (e.g., free recall, source recall, and old/new recognition) as well as semantic memory tasks (e.g., vocabulary and general knowledge questions), and each age group's performance on episodic and semantic tasks was compared. The results showed that on average, performance on episodic memory tasks declined steadily from adults aged 35-40 years to adults aged 75-80 years. Performance on semantic memory tasks, on the other hand, was fairly stable across age groups, thus suggesting that episodic memories are more susceptible to developmental declines due to normal aging than semantic memories.

Dual Memory Processes in Normal Aging

As pointed out before, normal aging seems to affect certain types of representations more than others. Specifically, representations that preserve meaning, or information learned a long time ago, are less susceptible to normal age-related interference than representations that preserve detailed, recently acquired information. Such a distinction about the content of representations is one that figures in contemporary dual-process theories (Brainerd & Reyna, 2010; Jacoby, 1991; Mandler, 1980; Wixted, 2007; Yonelinas, 2002), particularly in the fuzzy-trace theory (FTT; Reyna & Brainerd, 1995). According to the FTT, there are two distinct and independent types of mental representations, namely verbatim and gist. Verbatim traces are realistic representations of an item that preserve its surface features (e.g., color, font, and position) and whose retrieval is often accompanied by recollective phenomenology (i.e., vivid mental reinstatement of an item's prior occurrence). Gist

traces are impressionistic and fuzzy representations of the same item that preserve its bottom-line meaning instead (e.g., apple is an edible fruit), and therefore, it is thought to reflect an individual's understanding of the stimulus rather than the actual stimulus.

Similarly, in dual-process theories of recognition (Jacoby, 1991; Mandler, 1980; Wixted & Mickes, 2010; Yonelina, 2002), recognition is assumed to be controlled by recollection and familiarity. Although the major distinction between recollection and familiarity is phenomenological in nature—the former evokes vivid reinstatement on an item, whereas the latter does not—rather than about the content, as in FTT, it is generally assumed that recollection is more likely to control retrieval of detailed representations, such as contextual features of a stimulus, than familiarity (Yonelinas, 2002). More importantly, dual-process theories provide a framework to generate predictions about age-related changes in memory. For example, if normal aging hinders recollection / verbatim retrieval and spares familiarity / gist retrieval, it would be expected that performance on tasks that require retrieval of detailed memory traces ought to be more susceptible to the effects of aging than performance on tasks that do not.

In the recognition literature, the effects of aging on memory have been studied in two different but complementary ways, which over the course of roughly two decades, have produced findings that are consistent with dual-process predictions about normal aging. The first involves asking younger and older subjects to perform tasks that are slanted towards retrieval of one form of representation (e.g., surface and associative information) more than other (semantic), and then compare age-related differences across tasks. Consistent with the idea that normal aging affects detailed

representations more than semantic/conceptual ones, age-related differences in performance on recognition tasks that require retrieval of detailed information, such as associative recognition task, item-font/color recognition, recency judgments, or source recognition, are usually higher than age-related differences in performance on traditional old/new recognition (Naveh-Benjamin, 2000; Schacter, Harbluk, & McLachlan, 1984).

The second approach to the study of age-related declines in recognition tasks involves using mathematical models to separate the contribution of different retrieval processes to performance (Batchelder & Riefer, 1990; Brainerd et al., 2000; Wixted & Mickes, 2010; Yonelinas, 2002). Two of the most prominent methods, Tulving's (1985) remember/know (R/K) procedure and receiver operating characteristic curves (ROC; Yonelinas, 1994), use metacognitive judgments to measure dual processes. In the R/K procedure, for example, old/new decisions onn a recognition test are supplemented by judgments of remembering (R) and knowing (K). R judgments are made when features of a stimulus are consciously re-experienced during retrieval, while K judgments are made when subjects have knowledge about a stimulus' prior occurrence but do not consciously re-experience it during retrieval (Gardiner, 1988; Rajaram, 1993). During analysis, the proportion of R/K judgments are used to estimate recollection and familiarity parameters. When such an approach was used to investigate normal aging declines in recognition memory (e.g., Bastin & Van der Linden, 2003; Duarte, Henson, & Graham, 2008), as predicted, recollection estimates decreased with age but familiarity estimates were spared.

Unhealthy Aging and Memory

Chances are that at some point in life, we all had the unfortunate experience of forgetting where we left the keys to our car or house. For the most part, such events do not reflect deviations from normal aging and are in fact part of normal cognitive functioning. As shown next, it is when we start forgetting *what keys are for* that signals a change from normal aging to unhealthy aging.

Dementia, Alzheimer's disease, and mild cognitive impairment. Dementia refers to a non-specific clinical syndrome, in which there is large enough decline in memory and other cognitive functions (e.g., language, orientation) to compromise an individual's ability to function independently. It is estimated that dementia affects roughly 4.5 million adults aged 71 or older in the United States (Plassman et al., 2007), a number that is expected to increase up to three-fold by 2050 (Prince et al., 2013). (Of note, the term *dementia* has been recently removed from the DSM with the release of the 5th edition (American Psychiatric Association, 2013), and the condition it described now falls under a new category called *neurocognitive disorders*, which has a major and a minor sub-category in addition to the specification of its etiological subtype.) According to guidelines of the National Institute on Aging and the Alzheimer's Association (McKhann et al., 2011), there are five core clinical criteria for diagnosing dementia: (a) the symptoms interfere with the ability to function at work or at usual activities; (b) cognitive and behavioral symptoms represent a decline from prior level of functioning and performance; (c) the symptoms cannot be explained by delirium or other psychiatric disorder; (d) cognitive impairment is detected with a combination of the patient's history, as informed by the patient and a knowledgeable source, and objective cognitive examination; and (e) cognitive

impairment involves at least two domains, namely memory, reasoning, visuospatial abilities, language, and personality/comportment.

Alzheimer's disease (AD) is the most common cause of dementia and it involves a decline in episodic memory and at least one other cognitive area, such as language or executive functions (Reitz, Brayne, & Mayeux, 2011). It affects roughly 10% of the older adults in the United States (Brookmeyer et al., 2011) and it is characterized as an evolving process in which older adults who later develop AD usually go through a stage called mild cognitive impairment (MCI) first. Physiologically, AD is characterized by the accumulation of β-amyloid plaques in the brain, particularly in the hippocampus and entorhinal cortex, and the formation of neurofibrillary tangles composed of τ amyloid fibrils (Hardy, 2006).

The main hypothesis about the cause and progression of AD is the β-amyloid (Aβ) hypothesis (Hardy & Selkoe, 2002). Amyloid precursor protein (APP) is a membrane protein found in particularly large concentrations in the synapse of neurons, where they are thought to help the neuron grow and repair itself (Turner et al., 2003). As any other similar protein, it is used, broken down, and recycled, a process that is normally catalyzed by two types of enzymes, namely γ-secretase and α-secretase, which produces soluble peptide fragments that quickly go away. However, when β-secretase acts on the APP in conjunction with γ-secretase, they produce Aβ peptides, which are not very soluble (Aβ42 peptide being the least soluble one) and have a tendency to attach itself to other Aβ peptides, thus forming Aβ plaques that are characteristic of AD pathology, which interfere with the normal functioning of neurons, ultimately leading to the loss of neurons and then noticeable brain atrophy.

Unfortunately, it is not possible to confirm AD without brain tissue analysis, which is done postmortem, and for this reason, AD is always diagnosed as either *probable* AD or *possible* AD (McKhann et al., 2011). Probable AD is diagnosed when the following criteria are met: (a) the patient meets criteria for dementia; (b) symptoms have a gradual onset over months to years, rather than sudden; (c) there is a clear history of worsening of cognitive function; and (d) symptoms cannot be explained by a cerebrovascular disease, Lewy bodies, frontotemporal dementia, or other pathology. Possible AD is diagnosed when the patient meets the core clinical criteria for AD but some symptoms show an atypical pattern, such as sudden onset, or when there is not enough historical details or objective cognitive results indicating longitudinal declines in cognition, or when the patient meets criteria for AD as well as concomitant diseases that might be causing some of the symptoms (e.g., vascular dementia, Lewy bodies).

As mentioned before, MCI is a clinical state of cognitive decline between healthy aging and dementia in which cognitive impairment is greater than it would be expected for a subject's education level and age but not severe enough to be diagnosed as dementia (Samtani et al., 2013). It affects roughly 22% of older adults and has a yearly conversion rate to AD of about 12% (Petersen, 2004). Indeed, the main difference between MCI and dementia is on the level of impact that the symptoms have on daily life activities and work (McKhann et al., 2011). If the patient meets the core criteria for dementia but is able to continue functioning normally, the patient might be diagnosed as either amnesic MCI, if there is objective memory impairment, or non-amnesic MCI otherwise (Petersen, 2004). In previous studies, the amnesic

variety of MCI was found to be the more common of the two (Petersen et al., 2010) and more likely to progress to AD (Brainerd et al., 2013).

Dual processes in AD and MCI. Whereas normal aging affects episodic memory more than it affects semantic memory—and more specifically, retrieval of verbatim traces / recollection, rather than gist traces / familiarity—studies with AD patients tell a different story (Nebes, 1989; Salmon et al., 1999). In Budson et al. (2003), healthy older adults and AD patients studied lists of words (e.g., *sour, sugar, taste, candy*) semantically associated to a non-presented theme word (*sweet*). Afterwards, subjects received a recognition test composed of targets (*sour, taste*), related distractors (*sweet*), and unrelated distractors (*motorboat*), and they were instructed to accept previously studied items (old) and reject new ones (new). When younger and healthy older adults receive this same type of task, they often falsely recognize related distractors as targets, as related distractors cue retrieval of memory traces that preserve the bottom-line meaning of studied items, namely gist traces (Brainerd & Reyna, 2005; Roediger & McDermott, 1995). However, if AD patients have impaired gist/semantic memory, they should be less likely to falsely recognize related distractors than healthy, age-matched controls. Indeed, consistent with such prediction, AD patients in Budson et al.'s and other similar studies (Balota et al., 1999; Waldie & See, 2003; Watson, Balota, & Sergent-Marshall, 2001) were less likely to falsely recognize related distractors as targets than healthy controls.

As in healthy aging, although to a lesser extent, metacognitive judgments have also been used to measure recognition processes in unhealthy aging (Anderson et al., 2008; Smith & Knight, 2002). Koen and Yonelinas (2014) reviewed seven studies

that investigated recollection and familiarity in AD patients and age-matched controls, and nine studies that investigated recollection and familiarity in amnesic MCI and age-matched controls. Relative to healthy subjects, AD patients showed lower estimates of recollection as well as familiarity, while MCI patients showed lower estimates of recollection and spared familiarity, thus suggesting that at first, healthy to unhealthy transitions accelerate the normal age-related effect on episodic memory—that is, impaired recollection and spared familiarity—while further declines in unhealthy aging (MCI → AD) compromise familiarity as well as recollection.

However, as Brainerd et al. (2014) pointed out, metacognitive judgments are high-burden procedures that require subjects (a) to understand often detailed instructions about how to introspect on their retrieval phenomenology, (b) during the memory test, remember the instructions about the metacognitive judgments, and then (c) report on their introspections in a reliable fashion. It is not hard to see how such requirements can be a problem for clinical populations with impaired cognitive functions, as even healthy subjects often struggle with the very same high-burden procedures (Migo, Mayes, & Montaldi, 2012). In clinical populations with documented memory impairment, such as AD and MCI patients, there is an even higher chance that subjects may forget what characterizes R/K judgments, for example, which casts doubt on the assumption that the same processes are being measured between healthy and unhealthy subjects.

Instead of having subjects perform high-burden tasks to measure retrieval processes, Brainerd et al. (2014) proposed a low-burden procedure that does not require subjects to make any sort of metacognitive judgment; instead, subjects receive

multiple opportunities to study and recall lists of familiar words (e.g., *pie, shovel, home, three*), and then a mathematical model—the dual-retrieval model of recall (Brainerd, Reyna, & Howe, 2009; Gomes, Brainerd, & Stein, 2013; Gomes et al., 2014)—is applied to the data to extract simple measures of dual processes. Such a procedure should be well within the capabilities of AD and MCI subjects, as the very same task is part of standard clinical memory tests that are widely used with such a population. Examples of such clinical tests include the California Verbal Learning Test (Delis et al., 2000), the Rey Auditory Verbal Learning Task (Rey, 1941), the Consortium to Establish a Registry for Alzheimer's Disease (Morris et al., 1989), and the Alzheimer's Disease Assessment Scale (Rosen, Mohs, & Davis, 1984). Another advantage of the proposed approach is that its solution is analytical rather than methodological. That is, nothing new about the memory testing procedures that have been widely used to diagnose AD and MCI is introduced. The only change is the way the recall data are analyzed. Brainerd et al. took advantage of this to analyze clinical recall data from healthy, MCI, and AD subjects of two large-scale studies, namely the Aging, Demographic, and Memory Study (ADAMS; Plassman et al., 2007), and the Alzheimer's Disease Neuroimaging Initiative (ADNI; Mueller et al., 2005).

The ADAMS sample consisted of a nationally representative sample of older adults aged 70 years or older who received neuropsychological exams, including a clinical recall exam (CERAD), and were diagnosed as either healthy, MCI, or AD at regular intervals for over 6 years. Similarly, the ADNI sample was composed of older adults aged 55 years or older who were also diagnosed as either healthy, MCI, or AD, and received multiple neuropsychological testing at regular intervals for a period of 3

years. Contrary to the ADAMS sample, however, the ADNI sample was not representative but the clinical memory test they received (RAVLT) allowed Brainerd et al. (2014) to estimate dual retrieval processes for each individual, rather than diagnostic group, as in the ADAMS. In addition, contrary to the continuity hypothesis that unhealthy aging augments declines that are characteristic of normal aging—that is, declines in recollective process—as Koen and Yonelinas (2014) suggested, Brainerd et al. hypothesized that by the time MCI and AD subjects are diagnosed, measures of recollective process are already approaching near floor levels, only leaving room for nonrecollective process to change. Consistent with such idea, in the ADAMS, AD subjects had lower estimates of reconstructive recall, a nonrecollection process, than MCI and healthy subjects, while estimates of direct access, a recollective process, were low in absolute terms (M = .04) and very similar across diagnostic groups. In the ADNI sample, however, both recollective and nonrecollective recall processes showed reliable differences between healthy subjects and MCI subjects, as well as between MCI subjects and AD subjects. More importantly, however, when retrieval processes where used to predict transitions from healthy → MCI and MCI → AD, nonrecollective recall operations were the main reliable predictor.

The Present Studies

In my dissertation, I used Brainerd et al.'s (2014) approach to investigate longitudinal patterns of change in retrieval processes during healthy and unhealthy aging. The notion that AD is a neurodegenerative disease imply that its impact on cognitive functioning increases over time, which according to the Aβ hypothesis reflects the increasing accumulation of Aβ and hyperphosphorylated τ proteins in the

brain. Indeed, guidelines for diagnosing AD and MCI all emphasize that there should be objective evidence that declines in cognitive functioning should be relative to previous levels of functioning. It is well-documented that episodic memory declines with the progression of AD (Amieva et al., 2005; Sliwinski et al., 2003) but there is not a single study about which retrieval processes that control episodic memory decline. Of course, one natural hypothesis is that such declines are global memory declines that affect recollective and nonrecollective processes equally.

Another hypothesis, which is consistent with the notion of a qualitative shift in memory decline during unhealthy aging (Brainerd et al., 2009; Reyna & Brainerd, 2011), is that disease progression affects nonrecollective processes more than it affects recollective processes. In fact, if recollective retrieval is already too low by the time someone is diagnosed with AD, there will not be much left to lose in that domain. Furthermore, the notion of a qualitative shift in decline is consistent with Didic et al.'s (2011) hypothesis about the progression of τ pathology in AD. Specifically, Didic et al. proposed that in its early stages, AD-related lesions within the medial temporal are predominantly lesions in sub-hippocampal regions, rather than the hippocampus itself, and subjects with damage to the hippocampus but spared surrounding tissue show declines in recollective retrieval and episodic memory but spared familiarity and semantic memory (e.g., Aggleton et al., 2005; Lebrun-Givois et al., 2008). In order to test such hypothesis, the dual-retrieval model of recall was applied to the data from two longitudinal studies. The model is explained in more detail next.

Dual-Retrieval Model of Recall

Overview. In the dual-retrieval model, recall is controlled by three distinct and independent operations—direct access (*D*), reconstruction (*R*) and familiarity judgment (*J*)—that are measured with a two-stage Markov chain (Brainerd et al., 2009; Gomes et al., 2013). The model assumes that over study-test trials, studied targets transition through learning states whose entries are controlled by either a recollective process, direct access of targets' verbatim traces, or a nonrecollective one, reconstruction of targets from gist traces. Specifically, individual items transition through three discrete states: states U, P, and L. State U is a transient unlearned state, in which a target is never recalled. State P is a transient partially learned state, in which a target is recalled with probability equal to some value $0 < p < 1$. State L is an absorbing learned state, in which a target is always recalled. Before the first trial, targets begin in state U, as nothing has been learned about them. After the first trial, targets may transition from state U to either states P or L. After subsequent trials, targets may also transition from state P to L but once a target enters state L, it cannot leave it as long as the study-test trials continue.

Direct access controls retrieval from state L and is thought to retrieve a target's verbatim trace without comparing or searching through the traces of other items. In addition, direct access supports errorless recall because it allows subjects to simply read targets out of consciousness as their surface forms are mentally restored. Nonetheless, verbatim traces are more susceptible to sources of interference than are gist traces. In a free recall test, output interference makes direct access more likely to operate during the initial part of the free recall test than later on, thus constraining subjects' capacity to rely exclusively on direct access to recall list items (Barnhardt et

al., 2006). As subjects undergo additional trials, however, verbatim traces should become progressively less susceptible to interference.

Retrieval of a target in state P is controlled by reconstruction and a slave operation, familiarity judgment. Reconstruction controls entry into state P and is responsible for regenerating targets from partially identifying information, such as gist traces. Partially identifying information, however, can only provide a basis for reconstructing candidate items rather than identifying a specific one and therefore, it is necessary a slave operation to perform familiarity checks on reconstructed items. Specifically, the model assumes that subjects use an internal response criterion to evaluate which reconstructed items to output. Consequently, the nonrecollective form of recall (reconstruction + familiarity judgment) is an error-prone operation because it will at times generate and authorize output of new items.

The Markov chain. In the model, the probability of recalling a target is a function of direct access (D), reconstruction (R), and familiarity judgment (J). After an opportunity to study a list, the model posits that a target will be recalled if it occupies either the recollective state L, with probability D, or the nonrecollective state P_C, with probability $(1 - D)RJ$. Conversely, a target will not be recall if it occupies either state P_E, with probability $(1 - D)R(1 - J)$, or the state U, with probability $(1 - D)(1 - R)$. States U, P_E, P_C, and L are then mutually exclusive and exhaustive, as they describe all possible episodic states of a target immediately prior to recall. After a single study-test cycle, however, there will be only one empirical degree of freedom to estimate three free parameters, which makes the model's parameters unidentifiable in single-trial designs. The solution to this problem consists of defining the model over

multiple- rather than single-trial designs. In any recall paradigm in which subjects receive multiple study-test trials, as in this study, correct recall of a target on each test either occurs (C) or not (E). After *k* successive trials, targets generate a frequency distribution over 2^k possible error-success patterns across trials. For $k = 3$, for instance, a target will generate one out of the 8 error-success patterns, namely CCC, CCE, …, EEE. Such changes in recall over trials can be conceptualized as transitions through a discrete and finite state space, in which finite Markov chains (Kemeny & Snell, 1960) provide a natural formalism by assuming the following three properties. First, changes in recall over trials consists of making transitions through a finite set of discrete episodic states $\{\psi_1, \ldots, \psi_s\} \in \Psi$. Second, the state a target occupies on trial *n* (for $n = 1, \ldots, k$) depends only on the state it occupied immediately prior to the current state, $n - 1$. Third, at the level of individual targets, transitions through states between consecutive trials occur in an all-or-none fashion

Markov chains can be represented in terms of a unit starting vector, whose entries give the starting unconditional probabilities of each state, and one or more transition matrices, whose entries give the conditional probability of transitioning from state *i* on trial *n* - 1 to state *j* on trial *n*. In the dual-recall model, there are four mutually exclusive episodic states, namely $\{\mathrm{U}, \mathrm{P}_E, \mathrm{P}_C, \mathrm{L}\} \in \Psi$. Let $\mathbf{w}^{(1)} = [w_j^{(1)}]_{1x4}$ be a starting row vector with form

$$\begin{aligned} \mathbf{w}^{(1)} &= \left[P(L(1)), \quad P(P_E(1)), \quad P(P_C(1)), \quad P(U(1))\right] \\ &= \left[w_1^{(1)}, \quad w_2^{(1)}, \quad w_3^{(1)}, \quad w_4^{(1)}\right] \end{aligned}, \qquad (1)$$

and $\mathbf{M} = [m_{ij}]_{4x4}$ a transition matrix with form

$$\mathbf{M} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ m_{21} & m_{22} & m_{23} & m_{24} \\ m_{31} & m_{32} & m_{33} & m_{34} \\ m_{41} & m_{42} & m_{34} & m_{44} \end{bmatrix} = \left[\begin{array}{c|ccc} 1 & 0 & 0 & 0 \\ \hline \mathbf{a} & & \mathbf{T} & \end{array}\right], \quad (2)$$

in which $\mathbf{T}$ is a 3 x 3 sub-matrix of $\mathbf{M}$ whose entries give the probabilities of making transitions through transient states (U, P_E, and P_C) when a transition to the recollective and absorbing state L does not occur, and $\mathbf{a}$ is the 3 x 1 column sub-vector of $\mathbf{M}$ whose entries give the probability of transitioning from transient states on trial n - 1 to the state L on trial n. When Equations 1 and 2 are multiplied together, the entries of the resulting unit row vector $\mathbf{w}^{(n)} = [w_j^{(n)}]_{1x4}$ give the probability of a target occupying state j on trial n, as follows

$$\mathbf{w}^{(n)} = \mathbf{w}^{(1)} \times \mathbf{M}^{n-1}, \quad (3)$$

$$w_j^{(n)} = \begin{cases} w_j^{(1)}, & n = 1 \\ \sum_{i=1}^{4} w_i^{(n-1)} m_{ij}, & n > 1 \end{cases}. \quad (4)$$

Recall of a target occurs when it occupies either states L or P_C and therefore, Equations 3 and 4 provide a straightforward method for computing the probability of correct recall of a $_{\text{target}}$ on trial n. Let $P_n(Rc)$ be the correct recall probability on trial n be defined by the inner product of $\mathbf{w}^{(n)}$ and the vector $\mathbf{c} = [1, \ 0, \ 1, \ 0]$, such that

$$P_n(Rc) = \begin{cases} w_1^{(1)} + w_3^{(1)}, & n = 1. \\ w_1^{(n-1)} + \sum_{i=2}^{4} w_i^{(n-1)} (m_{i1} + m_{i3}), & n > 1 \end{cases} \quad (5)$$

Several possible parameterizations of the transition matrix **M** are possible (see Gomes et al., 2013). In this dissertation, I chose the one that has been often used in

previous studies (e.g., Brainerd et al., 2014; Gomes et al., 2013). The model version has two direct access parameters (D_1, D_2), two reconstruction parameters (R_1, R_2), and two familiarity judgment parameters (J_1, J_2), and is defined over a canonical study-test design of form $S_1T_1\,S_2T_2\,S_3T_3$, in which S is an opportunity to study and T to recall. The definition of each parameter is shown in Table 1. Additional model details are presented in the Appendix.

Study 1

The main objective of this study was to investigate changes in retrieval processes during healthy aging. Younger and older subjects received associative recall tasks and neuropsychological batteries at three different occasions over a period of roughly 1.5 years. The dual-retrieval model was applied to the recall data generated by each subject to estimate direct access, reconstruction, and familiarity judgment. As suggested by findings from prior studies, we expected that changes in recollective retrieval (direct access) would account for most of the developmental changes in recall performance between younger and older adults. Because subjects were for the most part healthy subjects, we did not expect to observe longitudinal declines in parameter estimates over a short period of 1.5 years. Nonetheless, there was enough variability in a marker of cognitive impairment—scores on the Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975)—to investigate its relationship with retrieval processes in recall. If there is a qualitative shift in memory declines with unhealthy aging, it would be expected to observe changes in reconstruction and familiarity judgment parameters, rather than direct access.

Methods

Design. The study consisted of a mixed longitudinal design in which two age groups (younger adults, older adults) were tested at three different time intervals (Waves A, B, and C), spanning roughly 18 months. On average, Wave B took place 10 months after Wave A, while Wave C took place 8 months after Wave B.

Subjects. A total of 253 older adults (M_{age} = 76 years, *SD* = 9.5 years; 177 females) and 180 younger adults (M_{age} = 20 years, *SD* = 1.2 years; 140 females) participated in Wave A. In Wave B, a total of 201 older adults (M_{age} = 76 years, *SD* = 9.1 years; 137 females) and 57 younger adults (M_{age} = 21 years, *SD* = 1.2 years; 49 females) who participated in Wave A were also recruited for Wave B. In Wave C, a total of 172 older adults (M_{age} = 76 years, *SD* = 9.1 years; 114 females) and 34 younger adults (M_{age} = 21 years, *SD* = 1.0 years; 29 females) who participated in Wave B were recruited for Wave C.[1]

Older adults were recruited from multiple facilities (e.g., universities, assisted living centers) in New York City, NY, and Tompkins County, NY, while younger adults were undergraduates recruited from Ithaca, NY. Summary statistics for additional demographic measures are shown in Table 2. For the most part, the sample of older adults was composed of retired, Caucasian adults who were married and highly educated—that is, had a Bachelor's degree or higher academic degree. The sample of younger adults was mainly composed of single, Caucasian undergraduates. Those demographic characteristics of the sample were stable across Waves A, B, and C.

Means and *SD*s for neuropsychological tests—namely, Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996), Shipley Vocabulary Test (SVT;

Shipley, 1940), Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975), and Prospective-Retrospective Memory Questionnaire (PRMQ; Smith et al., 2000)—are shown in Table 3. Inspection of Table 3 indicates that the two age groups were similar with respect to their scores on neuropsychological tests, including scores on the BDI, which were low in absolute terms (M_{BDI} = 6.9) and virtually identical. Indeed, in Wave A, an analyses of variance (ANOVA) on such data did not reveal any reliable difference between older and younger adults at the .05 significance level, except for the score on the SVT, $F(1, 297) = 25.44$, $MSE = 18.18$, $\eta_p^2 = .08$. Specifically, older adults scored higher on the SVT than younger adults (ΔSVT = 3.45), which is understandable given that the majority of the older adults continued their academic education beyond the undergraduate level. In Wave B, however, older adults scored lower on the MMSE than younger adults, $F(1, 133) = 18.51$, $MSE = 7.30$, $\eta_p^2 = .12$, and reported slightly more frequent prospective memory failures than younger adults, $F(1, 136) = 8.04$, $MSE = 21.84$, $\eta_p^2 = .07$. Similarly, in Wave C, older adults scored lower on the MMSE than younger adults, $F(1, 177) = 8.51$, $MSE = 6.52$, $\eta_p^2 = .05$. None of the other comparisons were reliable at the .05 significance level.

Lastly, summary statistics for the subjects' evaluation of their own health are shown in Table 4. As it can be seen in Table 4, the majority of the older and younger adults rated their health as either excellent or good, and save for use of psychotropic/antidepressant medication, nearly none of the subjects reported loss of consciousness, drug abuse, stroke, heart attack, Parkinson's disease, or chemotherapy. Such characteristics were also stable across Waves A, B, and C. Therefore, the

clinical variables indicated that older and younger adults who participated in this study were mainly healthy individuals.

The research protocol was approved by the institutional review board of all institutions involved. Written informed consents were obtained from all subjects prior to enrollment. Older adults who completed the study received a monetary compensation of $60, while younger adults received $25.

Materials and procedure. In Wave A, subjects received an associative recall task, followed by a battery of neuropsychological exams and questionnaires. The associative recall task was composed of two word lists (lists A and B), each containing 30 familiar and concrete word pairs (e.g., star -- pet, woman -- river), and it followed the same procedure that has been used in previous studies to measure retrieval processes in recall (Brainerd et al., 2014; Gomes et al., 2012, 2013). For each list, subjects received a non-canonical study (S) test (T) design of the form $S_1T_{1A}T_{1B}$ S_2T_2 S_3T_3. Prior to the first study-test cycle, subjects were told that they were going to be presented with several word pairs and they should pay close attention to them, as their memory for the word pairs would be tested afterwards. During the study phases, each word pair was presented on a computer screen for 4 seconds and read out loud by the researcher. During the test phases, the first word of each pair was presented for 5 seconds and subjects were instructed to recall the second word of each pair (e.g., star -- ?). Each study-test cycle was immediately followed by another study-test cycle until subjects reached the third and last one. After completing all study-test cycles for list A, subjects had a short break (5 min.) before starting list B. The presentation of each word pair on each list was randomized across study and test phases.

After the associative recall task, subjects received the neuropsychological battery. As before, the neuropsychological battery consisted of BDI (Beck, Steer, & Brown, 1996), SVT (Shipley, 1940), MMSE (Folstein, Folstein, McHugh, 1975), and PRMQ (Smith et al., 2000) (see Appendix). In the BDI, subjects are presented with 21 groups of short statements (e.g., *I do not feel sad, I feel sad much of the time, I am sad all the time, I am so sad or unhappy that I can't stand it*) and are instructed to pick the one that best describes the way they have been feeling recently. Its final score ranges from 0 to 63, with scores close to 0 indicating a low number of depressive symptoms, and scores close to 63 indicating a high number of depressive symptoms. In the SVT, subjects are presented with 40 target words (e.g., *talk*), each followed by four other words (e.g., *draw, eat, speak, sleep*), and subjects are instructed to indicate which of the four words has the same meaning as the target word next to it (*speak*). Performance on the SVT ranges from 0 to 40, in which 40 indicates all correct responses (i.e., excellent vocabulary) and 0 indicates none correct (poor vocabulary). In the MMSE, subjects are presented with a variety of questions and tasks related to functions such as attention, memory, language, and orientation, and therefore, the MMSE is frequently used as a marker of cognitive impairment. Its score ranges from 0 to 30, in which the lower the score is, the higher the level of cognitive impairment. The PRMQ is a self-rating scale that measures the reported frequency of retrospective memory failures (e.g., *Do you fail to recall things that have happened to you in the last few days?*) and prospective memory failures (*Do you forget to buy something you planned to buy, like a birthday card, even when you see the shop?*). Its final score

ranges from 0 to 80, in which the higher the score, the higher the frequency of reported memory failures.

Lastly, subjects were presented with a demographic questionnaire, followed by a health questionnaire. In the health questionnaire, subjects were instructed to rate their health in the past 2 months according to four subjective levels, ranging from *excellent* to *poor*. In addition, subjects were asked to report if they experienced loss of consciousness, alcohol/drug abuse, stroke, heart attack, Parkinson's disease, chemotherapy, or use of psychotropic/antidepressant medication in the past 6 months.

In Wave B, subjects received the associative recall task with new lists (lists C and D). In addition, after the recall task, subjects received a reduced neuropsychological battery composed of the MMSE and PRMQ, which was followed by the same health questionnaire used in Wave A. Similarly, Wave C included the associative recall task with new lists (lists E and F), the reduced neuropsychological battery, and the health questionnaire. List order was randomly assigned to each subject.

Results and Discussion

The present study sought to answer three main research questions. The first involved a comparison of the cross-sectional data of the study, namely whether recall operations differed between younger and older adults, which will tell us about the normal course of memory development from early to late adulthood. The second involved a comparison of the longitudinal data of the study, namely whether recall operations showed longitudinal changes across a period of 18 months. As it was pointed out before, developmental changes in cognition may occur in a relatively short

period of time. Finally, even though the majority of the older adults were healthy, some showed declines in one of the most commonly used marker of cognitive impairment—the MMSE. Therefore, the third question was whether recall operations were related to changes in a marker of cognitive impairment later in life.

The results were organized as follows. First, I reported findings from the analyses of subjects' overall performance on the associative recall tests. Second, I applied the dual-retrieval model to the recall data generated by younger and older adults to estimate three operations that control recall, namely direct access, reconstruction, and familiarity judgment. In both cases, I used a multilevel linear model (MLM; Laird & Ware, 1982) to investigate longitudinal patterns of change and differences in age groups and levels of other variables of main interest, namely older adults' age and score on the MMSE. The MLM applied to the longitudinal data was the following:

$$y_{ij} = \pi_{0i} + \pi_{1i}(time_{ij}) + \varepsilon_{ij}, \tag{6}$$

in which y_{ij} is the dependent variable (e.g., overall recall, direct access, reconstruction, familiarity judgment) for the i^{th} subject and j^{th} wave, π_{0i} is the individualized y at the baseline, π_{1i} is the individualized rate of change in y for every unit change in time (years), and ε_{ij} is the residual. For all subjects, π_{0i} and π_{1i} are defined as follows

$$\begin{cases} \pi_{0i} = \gamma_{00} + \gamma_{01}(age\ group_{ij}) + \gamma_{02}(old\ age\ at\ baseline_{ij} - 75) \\ \qquad\qquad + \gamma_{03}(30 - MMSE_{ij}) + e_{0i} \\ \pi_{1i} = \gamma_{10} + \gamma_{11}(age\ group_{ij}) + \gamma_{12}(old\ age\ at\ baseline_{ij} - 75) \\ \qquad\qquad + \gamma_{13}(30 - MMSE_{ij}) + e_{1i} \end{cases}, \tag{7}$$

in which γ_{00} is the mean of y at baseline for younger adults; γ_{01} is the average change in γ_{00} if the subject is an older adult, while holding both MMSE (30) and age at baseline (centered around the group mean age, 75 years) constant; γ_{02} is the average change in $\gamma_{00} + \gamma_{01}$ for every unit change from 75 years in an older adult's age at baseline, while holding MMSE constant (30); γ_{03} is the average change in $\gamma_{00} + \gamma_{01}$ for every unit decrease from 30 in an older adult's MMSE score, while holding age at the baseline constant (75 years); γ_{10} is the average rate of change in y for every unit change in time (years) for younger adults; γ_{11} is the average change in γ_{10} if the subject is an older adult, while holding both MMSE (30) and age at baseline (75 years) constant; γ_{12} is the average change in $\gamma_{10} + \gamma_{11}$ for every unit change from 75 years in an older adult's age at baseline, while holding MMSE constant (30); γ_{13} is the average change in $\gamma_{10} + \gamma_{11}$ for every unit decrease from 30 in an older adult's MMSE score, while holding age at the baseline constant (75 years); e_{0i} is the within-individual error in y at baseline; and e_{1i} is the within-individual error in the rate of change in y across time. Variance and covariance parameters were estimated with an autoregressive covariance structure with homogeneous variance parameters. For all statistical tests, a .05 significance level was used.

Recall performance. The mean correct recall is shown in Table 5 as a function of test, list order, age group, and wave. Inspection of the overall recall performance in Table 5 shows that overall recall was fairly similar between list 1 (*M* = .59) and list 2 (*M* = .64) but regardless of list and testing wave, older adults recalled fewer words (*M* = .43) than younger adults (*M* = .80). To investigate whether age group differences were reliable, as well as possible longitudinal patterns of change in

overall recall, I fit the MLM in Eq. 6 and Eq. 7 to the observed data. The maximum likelihood estimates of each parameter of the model are shown in Table 7. There was a reliable effect of age group, older adults' MMSE score, and older adults' age at baseline. On average, older adults recalled fewer words than younger adults, and such an effect increased as (a) older adults' age increased and (b) their MMSE decreased. In addition, regardless of age group, subjects' recall performance was stable across Waves A, B, and C, as shown in Figure 1, which contains the predicted levels of correct recall as a function of age group and waves.

Model-based analysis. The dual-retrieval model was applied to the frequency of recall patterns that each subject generated across tests $T_{1a/1b}$ T_2 T_3 to obtain individualized estimates of direct access (D_1, D_2), familiarity judgment (J_1, J_2), and reconstruction (R_1, R_2) parameters. Because there are seven independent empirical probabilities (8 recall patterns – 1) and six free parameters in the model, the model generates a G^2 statistic with 1 degree of freedom, which is asymptotically distributed as a $\chi^2(1)$ that has critical value of 3.84 to reject the null hypothesis of fit. The distribution of the G^2 statistic, across all lists and waves, is shown in Figure 2 for younger adults and Figure 3 for older adults, in which the solid vertical line indicates the mean and the dashed vertical line indicates the critical value to reject the null hypothesis of fit. In both groups, the mean $G^2(1)$ statistic was well below the critical value (2.36 for younger adults, and 2.61 for older adults), thus indicating that the dual-retrieval model provided close description of the recall data that most subjects generated.

The maximum likelihood estimate of each parameter of the model is shown in Table 7. Close inspection of Table 7 suggests that the main process locus of the age group differences in recall is the direct access operation. Specifically, regardless of list and wave, both direct access parameters were consistently higher for younger adults (M = .47) than older adults (M = .17). However, age group differences in reconstructive recall seemed to shift as a function of study-test cycles. More specifically, at the beginning of the study-test cycles, younger adults were better able to reconstruct studied words (M_{R1} = .62) than older adults (M_{R1} = .33) but older adults were more willing to output a reconstructed word (M_{J1} = .78) than younger adults (M_{J1} = .58); as the study-test cycles continued, older adults were better able to reconstruct studied words (M_{R2} = .57) than younger adults (M_{R2} = .43). Nonetheless, the latter interaction is likely due to the fact that there were not many words left at the end of the study-test cycles for younger adults to recall reconstructively. In Table 5, notice that younger adults' recall on T_3 approached ceiling, whereas older adults' recall was slightly higher than 50% on the same test. In other words, by the end of the three study-test cycles, older adults were still learning to recall studied words reconstructively, while younger adults had already learned to recall nearly the entire list recollectively. As before, to check the reliability of such differences and possible longitudinal patterns of change, I fit the MLM in Eq. 6 and Eq. 7 to the estimates of each parameter. The results are shown in Table 6.

As expected, inspection of Table 6 reveals that there was a reliable effect of age group in both direct access parameters, both reconstruction parameters, and familiarity judgment on the first study-test cycle. Interestingly, the effect of MMSE

was only reliable on D_2 and R_2 estimates—that is, at the beginning of the study-test cycles, there was no evidence that MMSE affected recall operations but as the study-test cycles continued, the lower the MMSE score was, the lower was the older adult's ability to recall either recollectively or reconstructively. Older adults with a MMSE score of 22, for example, had lower estimates of D_2 (.13) and R_2 (.51) than older adults with a MMSE score of 28 (D_2 = .26; R_2 = .59).

In addition, older adults' age showed a reliable effect on both direct access parameters and on reconstruction on the first study-test cycle. Therefore, healthy older adults aged 70 years, for example, had higher D_1 (.11), D_2 (.30), and R_1 (.36) than healthy older adults aged 80 years (D_1 = .07; D_2 = .22; R_1 = .31). Finally, there was a small but reliable longitudinal effect on D_1: for every year past Wave A, there was an average increase of .05 in D_1. Such a finding was not expected but suggests that as subjects became more familiar with the study protocol, for example, there was less interference (or lower cognitive load) to affect direct retrieval of an item's verbatim traces. Nonetheless, it was a small effect and for the most part, recall operations were quite stable across a period of 18 months.

Summary. Direct access was the primary process locus of healthy developmental changes in recall. Specifically, even though healthy older adults were able to recall studied items recollectively (direct access) and reconstructively (reconstruction + familiarity judgment), younger adults were much better at learning to recall studied items recollectively right away, and whatever item they had not recalled recollectively, they were better able to recall them reconstructively than older adults, but this latter effect was smaller than the former. In addition, regardless of age

group, retrieval processes in recall were fairly stable across a period of 18 months. For example, if some subjects were able to recall most of the studied items recollectively during Wave A, they usually tended to do the same in Waves B and C at a very similar rate.

Concerning older adults, the results showed that changes in a marker of cognitive impairment—MMSE—were related to changes in reconstruction and direct access after the first study-test cycles. Older adults who scored lower on the MMSE (e.g., 24) had lower estimates of R_2 and D_2 than older adults who scored higher on the MMSE (28). Finally, subjects' age affected direct access and reconstruction. Specifically, older adults aged 80 years, for example, were less able to use direct access and reconstruction early on in the study-test cycles than older adults aged 70 years.

Study 2

In the previous study, the focus was on developmental changes in retrieval processes that are expected to occur in normal aging, as for the most part, subjects were healthy adults. Later in life, however, memory becomes ever more susceptible to diseases that cause dementia, Alzheimer's disease being the most common one (Hebert et al., 2003). In this second study, I investigated how AD and its prodromal stage, amnesic MCI (Petersen, 2004), affected retrieval processes. This was accomplished with the analysis of a large-scale clinical database from the Alzheimer's Disease Neuroimaging Initiative (ADNI; Mueller et al., 2005). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private

pharmaceutical companies and non-profit organizations, as a $60 million, 5- year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

In the present study, only data from the ADNI-1 protocol were used, as it was the only protocol that contained itemized recall data suitable for model-based analysis. In the ADNI-1 protocol, subjects participated in eight sessions spanning 36 months, namely screening, baseline, month 6, month 12, month 18, month 24, month 30, and

month 36. However, recall data were only collected in six of those sessions—namely, baseline, month 6, month 12, month 18, month 24, and month 36—and therefore, they were the primary focus in the present study.

Methods

Subjects. As before, ADNI subjects were recruited from multiple sites across the U.S. and Canada. The main eligibility criteria for enrolled subjects were the following: (a) between 55 and 90 years of age; (b) there is someone who can act as a proxy to provide independent evaluation of functioning; (c) subject speaks English or Spanish; (d) must be willing and able to undergo all test procedures during each follow-up session; and (e) subject is not currently using specific psychoactive medication(s) that might interfere with the outcome of the study procedures. The main exclusion/inclusion criteria for healthy controls (HC), MCI subjects, and AD subjects are shown in Table 8. As indicated on Table 4, MCI subjects were amnestic MCI subjects (Petersen, 2004), and AD subjects were probable AD subjects (McKhann et al., 2011). The number of subjects who were either diagnosed with MCI or AD, or classified as HC, is shown in Table 9 as a function of session number.

In the baseline session, the sample size consisted of 748 older adults (433 males) aged 75 years on average (*SD* = 6.8 years). It the month 6 session, the sample size consisted of 717 older adults (417 males) aged 75 years on average (*SD* = 6.8 years). In the month 12 session, the sample size consisted of 717 older adults (394 males) aged 75 years on average (*SD* = 6.7 years). In the month 18 session, which was exclusive for subjects who had been diagnosed with MCI, the sample size consisted of 306 older adults (198 males) aged 77 years on average (*SD* = 6.6 years).

In the month 24 session, the sample size consisted of 594 older adults (342 males) aged 77 years on average (*SD* = 6.6 years). Finally, in the month 36 session, the sample size consisted of 409 older adults (243 males) aged 78 years on average (*SD* = 6.3 years).

Summary statistics of additional demographic variables are shown in Table 10 as a function of diagnostic group at the baseline. Inspection of Table 10 indicates that on average, subjects were well-educated, married, and Caucasian older adults. Regarding cognitive impairment, summary statistics of the scores on the MMSE are shown in Table 11 as a function of session and diagnostic group. As expected, regardless of the session, scores on the MMSE were different between diagnostic groups at the .05 level of significance, Fs ≥ 53.87. Specifically, healthy subjects were less cognitively impaired than MCI subjects (ΔMMSE = 2.22), and MCI subjects were less cognitive impaired than AD subjects (ΔMMSE = 4.99).

Materials and procedure. Subjects received clinical and cognitive evaluations at specific time intervals, as indicated on Table 12. HC subjects were studied at 0, 6, 12, 24, and 36 months; MCI subjects were studied at 0, 6, 12, 18, 24, and 36 months; and AD subjects were studied at 0, 6, 12, and 24 months. (Notice, however, that the original study contained cognitive, biological, and imaging measures that were not investigated in the present study and therefore, were omitted from Table 9. For the complete schedule and description of other materials and procedures, see Weiner et al., 2014, for example.) During the screening and baseline, subjects received a brief explanation of the ADNI-1 protocol, provided demographic information, and received a battery of neuropsychological tests. The

neuropsychological battery consisted of the Rey Auditory Verbal Learning Task (RAVLT; Rey, 1940), MMSE (Folstein, Folstein, McHugh, 1975), digit span tasks, Alzheimer's Disease Assessment Scale (Rosen et al., 1984), Wechsler Memory Scale (Wechsler, 1997), Boston Naming Test (Kaplan, 1983), Clocks Test, Category Fluency Test, Neuropsychiatric Inventory (Cummings et al., 1994), Clinical Dementia Rating (Morris, 1993), and the Geriatric Depression Scale (Yesavage et al., 1983).

The RAVLT is an episodic memory test that measures the ability to recall 15 familiar words (e.g., *honey*, *pie*, *table*, *clock*, etc.) across five study (S) test (T) cycles (S_1T_1 S_2T_2 S_3T_3 S_4T_4 S_5T_5), two delayed recall tests, and a final recognition test. Prior to the first study-test cycle, subjects are told to listen carefully to the words the examiner will read, as soon afterwards, they will be asked to recall as many of those words as possible, in whatever order they choose. After the fifth study-test cycle on the target list, subjects received a new study-test cycle on a new word list (e.g., *car*, *tree*, *task*, *flower*, etc.)—the interference list. After a single study-cycle on the inference list, subjects received two delayed recall tests on the target list (*honey*, *pie*, *table*, *clock*, etc.): one immediately after the study-cycle on the interference list, and another 30 min. afterwards. At the end, subjects receive a recognition test containing old words (e.g., *pie*, *clock*) and new ones (e.g., *plane*, *apple*).

Results and Discussion

There were two main objectives in the analysis of the ADNI-1 RAVLT data. The first was to investigate process-level differences between HC and MCI subjects, and between MCI and AD subjects. The second was to investigate longitudinal patterns of change in retrieval processes as a function of diagnostic group (HC, MCI,

AD). As before, the results were organized in two parts, that is, findings from the analysis of overall recall performance and findings from the analysis of process-level measures (direct access, reconstruction, and familiarity judgment). Similar to the previous study, there were several limitations in using traditional statistical techniques (e.g., repeated measures ANOVA, multiple regression) for the analysis of the ADNI data, owing to the nature of the longitudinal design. For example, some subjects dropped out before the last session, repeated measures were not independent from one another, the number of sessions was conditional on diagnostic group, and subjects were sometimes unable to complete the RAVLT or other exams. Therefore, a MLM was used to model diagnostic group differences and longitudinal patterns. The MLM used to analyze the ADNI data was the following:

$$y_{ij} = \pi_{0i} + \pi_{1i}(time\ HC_{ij}) + \pi_{2i}(MCI_{ij}) + \pi_{3i}(time\ MCI_{ij}) + \pi_{4i}(AD_{ij}) + \pi_{5i}(time\ AD_{ij}) + \varepsilon_{ij}, \quad (8)$$

in which y_{ij} is the dependent variable for the i^{th} subject and j^{th} month, π_{0i} is the HC individualized y at baseline, π_{1i} is the HC individualized rate of change in y for every unit change in time *since the subject was first diagnosed as* HC (years), π_{2i} is the change in π_{0i} if the subject was diagnosed as MCI, π_{3i} is the MCI individualized rate of change in y for every unit change in time *since the subject was first diagnosed as* MCI (years), π_{4i} is the change in π_{0i} if the subject was diagnosed as AD, π_{5i} is the AD individualized rate of change in y for every unit change in time *since the subject was first diagnosed as* AD (years), and ε_{ij} is the residual. The key difference, relative to Eq. 1, is that the definition of time is not the same now: *time* is the amount of time

since the subject was first diagnosed as either HC, MCI, or AD. Such a distinction is crucial because subjects in the ADNI often transitioned from one diagnostic group to another. (In fact, the majority of such transitions were from MCI→AD, as HC→MCI/AD, MCI→HC, AD→MCI/HC, or any other transitions, were rare within the 36 months period investigated in the present study.) The level 1 parameters $\pi_{0i}, \pi_{1i}, \pi_{2i}, \pi_{3i}, \pi_{4i},$ and π_{5i} are defined as follows

$$\begin{cases} \pi_{0i} = \gamma_{00} + \gamma_{01}(age_{ij} - 75) + e_{0i} \\ \pi_{1i} = \gamma_{10} + \gamma_{11}(age_{ij} - 75) + e_{1i} \\ \pi_{2i} = \gamma_{20} + \gamma_{21}(age_{ij} - 75) + e_{2i} \\ \pi_{3i} = \gamma_{30} + \gamma_{31}(age_{ij} - 75) + e_{3i} \\ \pi_{4i} = \gamma_{40} + \gamma_{41}(age_{ij} - 75) + e_{4i} \\ \pi_{5i} = \gamma_{50} + \gamma_{51}(age_{ij} - 75) + e_{5i} \end{cases}, \quad (9)$$

in which γ_{00} is the mean y when a HC subject was first diagnosed as HC; γ_{01} is the average change in γ_{00} for every unit change from 75 years in a subject's age when first diagnosed as HC (i.e., *age* was centered around the sample mean, 75 years); γ_{10} is the average rate of change in y for every unit change in time diagnosed as HC, while holding the age first diagnosed as HC (75 years) constant; γ_{11} is the average change in γ_{10} for every unit change from 75 years in a subject's age when first diagnosed as HC; γ_{20} is the average change in γ_{00} if the subject was diagnosed as MCI; γ_{21} is the average change in γ_{20} for every unit change from 75 years in a subject's age when first diagnosed as MCI; γ_{30} is the average rate of change in y for every unit change in time diagnosed as MCI, while holding the age first diagnosed as MCI (75 years) constant; γ_{31} is the average change in γ_{30} for every unit change from 75 years in a subject's age when first diagnosed as MCI; γ_{40} is the average change in γ_{00} if the

subject was diagnosed as AD; γ_{41} is the average change in γ_{40} for every unit change from 75 years in a subject's age when first diagnosed as AD; γ_{50} is the average rate of change in y for every unit change in time diagnosed as AD, while holding the age first diagnosed as AD (75 years) constant; γ_{51} is the average change in γ_{50} for every unit change from 75 years in a subject's age when first diagnosed as AD; and $e_{0i}, e_{1i}, e_{2i}, e_{3i}, e_{4i},$ and e_{5i} are error terms for their respective level 2 variable. As in the previous study, an autoregressive covariance structure with homogeneous variance parameters was used to estimate the variance and covariance parameters. For all statistical tests, a .05 significance level was used.

Recall performance. Summary statistics for overall recall across the learning trials of the RAVLT (S_1T_1 S_2T_2 S_3T_3 S_4T_4 S_5T_5) are is shown in Table 13 as a function of diagnostic group (HC, MCI, AD) and session (baseline, month 6, month 12, month 18, month 24, month 36). Inspection of the group averages presented in Table 13 suggests that regardless of session, HC subjects recalled more words on the RAVLT (*M* = .58) than MCI subjects (*M* = .40), and MCI subjects recalled more words than AD subjects (*M* = .28).

The MLM in Eq. 8 and 9 was fit to the overall recall data from the ADNI-1 protocol to generate maximum likelihood estimates of its parameters, which are shown in Table 14. As expected, the effects of diagnostic group on correct recall were all reliable—that is, MCI subjects recalled fewer words than HC subjects, and AD subjects recalled even fewer words than MCI subjects. In addition, there was a reliable longitudinal effect of MCI on correct recall, and a reliable longitudinal effect of AD on correct recall. As long as subjects remained healthy, there was no evidence

of longitudinal changes in correct recall. However, in the MCI group, correct recall decreased as function of time diagnosed as MCI, and similarly, in the AD group, correct recall decreased as a function of time diagnosed as AD. In other words, the longer subjects were diagnosed as either MCI or AD, the worse their recall performance became, and the longitudinal decline was larger in the AD group than in the MCI group.

Furthermore, in the AD group, there as a small but reliable interaction between the age that the subject was diagnosed with AD and the magnitude of the longitudinal decline in recall performance. Specifically, the older subjects were diagnosed with AD, the larger the longitudinal declines in recall. For example, older adults first diagnosed with AD when they were 85 years old showed higher declines in recall across the next years than older adults first diagnosed with AD when they were 70 years old. Similarly, even though HC subjects did not show reliable longitudinal changes in correct recall, there was a small but reliable effect of HC subjects' age on correct recall, namely older HC subjects (e.g., 80-years-old) recalled fewer words than younger HC subjects (e.g., 70-years-old).

Model-based analysis. The learning trials on the RAVLT (S_1T_1 S_2T_2 S_3T_3 S_4T_4 S_5T_5) generate 2^5 recall patterns (CCCCC, CCCCE, …, EEEEE) and because the word list contains 15 words, it is not possible to fit the dual-retrieval model to the frequency of recall patterns of each subject without greatly compromising the reliability of parameter estimates, as at least 17 of those recall patterns will have zero frequency, and the remaining ones will have a very small frequency. One possible solution is to collect data from multiple lists instead of one, but this can be exhausting

for the subject and a lengthy process overall. Fortunately, another solution has been proposed in previous studies (e.g., Brainerd et al., 2014) that does not involve any change in procedure. Specifically, the problem with long sequences of recall patterns can be dealt with by using a sliding window bootstrapping procedure, in which learning trials are first partitioned into three shorter sequences of consecutive trials, namely $T_1T_2T_3$, $T_2T_3T_4$, and $T_3T_4T_5$, and then the frequency of recall patterns are summed across the three sequences, under the assumption that any given recall operation (e.g., the three D_1 parameter estimates for sequences $T_1T_2T_3$, $T_2T_3T_4$, and $T_3T_4T_5$) is correlated across neighboring trials (Gomes et al., 2013). In the present study, the latter strategy was used to fit the dual-retrieval model to the recall data from the RAVLT.

Fit tests showed that the dual-retrieval model provided close description of the individualized data of HC, MCI, and AD subjects. For each subject, application of the model to the RAVLT data generated a G^2 statistic, which is asymptotically distributed as $\chi^2(1)$ with critical value of 3.84 to reject the null hypothesis of fit. The distribution of the G^2 statistic across all subjects and sessions is shown in Figure 3 for HC subjects, Figure 4 for MCI subjects, and Figure 5 for AD subjects. In all three diagnostic groups, the mean G^2 statistic was well below the critical value and similar across groups (1.43 for HC subjects, 1.42 for MCI subjects, and 1.34 for AD subjects). Altogether, the goodness of fit tests indicated that the model provided a good description of the RAVLT data, regardless of whether the subject was a HC subject, a MCI subject, or an AD subject.

Regarding means of the maximum likelihood estimates of the dual-retrieval model's parameters, they are shown in Table 15 as a function of diagnostic group and session. Inspection of the averages in Table 15 suggests process-level differences between diagnostic groups. Regardless of session, direct access parameters decreased from HC subjects (mean D = .23) to MCI subjects (mean D = .13) to AD subjects (mean D = .08). Interestingly, process-level differences in nonrecollective parameters (reconstruction and familiarity judgment) were not all across the board. While reconstruction on the first few study-test trials (R_1) was similar between HC subjects (.41) and MCI subjects (.38), it was lower in AD subjects (.32). Reconstruction after the first study-test trials (R_2), however, declined sharply from HC subjects (.38) to MCI subjects (.22), and then seemed to decline even further in comparison to AD subjects (.13). Similarly, both familiarity judgment parameters declined from HC subjects (mean J = .66) to either MCI subjects (mean J = .56) or AD subjects (mean J = .51), but they were relatively similar between the latter two diagnostic groups.

Next, the MLM in Eq. 8 and 9 was fit to the data in order to obtain maximum likelihood estimates of the MLM's parameters. The result is shown in Table 14. As expected, differences across diagnostic groups were all reliable except for R_1 between the HC and MCI groups and J_2 between MCI and AD groups. Importantly, there were reliable longitudinal declines in parameter estimates in the MCI and AD groups. More specifically, in MCI subjects, reconstruction after the first few study-test trials (R_2) decreased significantly as a function of time subjects remained diagnosed as MCI. In the same vein, in AD subjects, reconstruction during the first few study-test trials (R_1), as well as direct access (D_1), decreased significantly as a function of time subjects

remained diagnosed as AD. In HC subjects, however, retrieval processes were fairly stable through the years, as long as subjects remained diagnosed as HC.

In addition, there were reliable effects of age on parameter estimates. More specifically, in HC subjects, age affected both direct access parameters and no other operations—that is, on average, older HC subjects recalled fewer words recollectively than younger HC subjects. Similarly, in both MCI and AD subjects, the age that the subjects were first diagnosed affect direct access during the first few study-test trials (D_1). Specifically, on average, older MCI and AD subjects recalled fewer words recollectively on the first few tests of the RAVLT than their younger counterparts.

When the estimates in Table 14 were plugged into Eq. 8 and 9 of the MLM, it was possible to generate predicted values of retrieval operations as a function of time with a diagnosis and diagnostic group. Such predicted values are shown in Table 16, while holding the age that subjects were first diagnosed constant (75 years). According to the MLM, in the span of three years, AD subjects were expected to show a 29% decrease in D_1 and a 38% decrease in R_1 as long as they remained with AD. Similarly, MCI subjects were expected to show a 22% decrease in R_2 as long as they remained with MCI. As long as HC subjects remained healthy, on the other hand, their retrieval processes were not expected to show significant changes through the years.

Summary. Regarding differences between healthy subjects (HC) and unhealthy subjects (MCI/AD), on average, HC subjects had higher estimates of recollective recall (direct access), as well as reconstructive recall (reconstruction + familiarity judgment), than MCI/AD subjects. However, in the span of three years,

while retrieval processes showed reliable longitudinal declines in MCI/AD subjects, the very same processes were quite stable in HC subjects, as long as they remained healthy. Specifically, in MCI subjects, reconstruction after the first few study-test trials declined steadily the longer subjects remained in the MCI group, and in AD subjects, reconstruction and direct access during the initial trials declined steadily the longer subjects remained in the AD group. For one, such a finding is consistent with the idea that MCI and AD are neurodegenerative clinical disorders—that is, they involve a gradual loss of structure/function over time—and that the longer subjects remain in one or the other condition, the easier it should be to differentiate their clinical condition. More importantly, they suggest that some processes decline faster than others in MCI and AD, which can be seen as a process-level signature of each clinical condition.

Subjects' age showed reliable effects on direct access parameters as well. Older HC subjects had lower direct access than younger HC subjects. In MCI and AD subjects, age also affected direct access but it was only reliable for direct access during the first few study-test cycles.

General Discussion

The main objective of my dissertation was to extend current work on dual-retrieval processes of recall to areas of healthy and unhealthy memory declines that had not been addressed before. In the first study, direct access, reconstruction, and familiarity judgment were measured in samples of younger and older healthy adults who were followed for a period of roughly 18 months. As expected, younger adults performed better on associative recall tasks than older adults. It was hypothesized that

such declines would reflect primarily declines in recollective retrieval, and consistent with such hypothesis, declines in direct access accounted for most of the differences in recall between younger and older healthy adults. After a single opportunity to study and to recall a list of familiar words, younger adults recalled more words recollectively than older adults, and as subjects moved from one study-test cycle to another, younger adults were faster at learning to recall additional words recollectively than older adults. In fact, by the time subjects finished all study-test cycles, younger adults' recall approached ceiling, while older adults were still trying to recall roughly half of the studied items—as before, such difference was primarily in the recollective retrieval domain. Furthermore, as long as subjects remained healthy, their preferred mode of retrieval remained quite stable over a period of 1.5 years.

In the first study, therefore, the story about healthy memory declines from early to late adulthood was straightforward: recall decreased from early to late adulthood, and such decreases had a primary process locus, namely recollective retrieval. One line of investigation suggests that age-related declines in recollective retrieval reflect developmental changes in encoding. Older adults are less likely to report the use of encoding strategies that facilitate retrieval (elaborative and associative encoding) than younger adults, and when subjects are unaware of a follow-up memory test, age-related differences in performance tend to decrease (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000; Perfect & Dasgupta, 1997). For example, it is possible that younger subjects were more likely to use encoding strategies to connect words from each pair than older adults (e.g., encode the word pair *knight—tooth* as *the knight who lost his tooth*), or paid more attention to both words of each pair rather than

one or the other. Another explanation, which does not exclude possible developmental changes in encoding, is that normal age-related declines in recollective retrieval are associated with structural changes that occur in the hippocampus with advancing age (Golomb et al., 1994; Moscovitch & Winocur, 1992; Raz et al., 1998). Fjell et al. (2009), for example, found that in healthy older adults, the hippocampus shows the largest rate of volume reduction per year (see also Raz et al., 2005).

Of note, although the sort of memory declines previously reported were declines in memory for relatively simple stimuli (e.g., words), prior studies have shown that healthy older adults also remember fewer complex, real-life events (e.g., meetings and events of personal relevance, a trip or journey) than younger adults (Martinelli et al., 2013; Piolino et al., 2002; Piolino, Desgranges, & Eustache, 2009). In addition, consistent with the notion that normal aging impairs recollective retrieval more than nonrecollective retrieval, autobiographical memory studies suggest that healthy aging impairs retrieval of detailed memories more than it impairs retrieval of general memories. Levine et al. (2002), for example, asked younger and older healthy adults to report events from different life periods, which were segmented and categorized into internal details and external details. Internal details included those directly related to the main event described by the subject (e.g., when and where the event took place, what someone was doing or wearing), while external details included those that were not directly related to the main event and were primarily semantic in nature (e.g., facts, definitions, names). If normal aging foments a shift from retrieval of detailed representations towards retrieval of more abstract traces of past experiences, it would be expected that younger adults would report more internal

details and less external (semantic) details than older adults. That was the exact pattern reported. On average, older adults recalled fewer internal details than younger adults but the number of external details recalled by older adults was even higher than the number recalled by younger adults, regardless of whether the events were emotional or not (St. Jacques & Levine, 2007).

Even though older adults from the first study were healthy subjects for the most part—that is, they reported hardly any history of health conditions that could affect performance, had high scores on the MMSE, and very small number of depressive symptoms—variability on the MMSE was large enough to allow analysis of possible correlates with retrieval processes. Here, one hypothesis that was tested was whether there were qualitative shifts in the form of memory declines, relative to what we observed during healthy aging (Reyna & Brainerd, 2011; Reyna & Mills, 2007). If cognitive impairment late in life just accelerates the developmental trajectory of normal age-related changes in memory, then recollective retrieval declines should be larger than nonrecollective retrieval declines and more likely to be associated with markers of cognitive impairment than nonrecollective retrieval. There was no evidence supporting such idea. Increased cognitive impairment late in life, as assessed by declines in the MMSE, was similarly related to direct access and reconstruction. For every unit decrease from 30 in the MMSE score, direct access and reconstruction after the first study-test trial decreased roughly 2%. Therefore, the process-level signature of normal age-related declines—big declines in direct access—was not the same marker of cognitive impairment.

In the second study, I continued to investigate changes in retrieval processes in unhealthy aging, but contrary to the previous study, now such changes were investigated in clinical samples of AD patients, MCI patients, and healthy, age-matched controls. Relative to unhealthy older adults, healthy older adults had higher estimates of recollective recall (direct access) and reconstructive recall (reconstruction + familiarity judgment). Relative to AD patients, MCI patients had higher estimates of reconstructive recall and similar estimates of direct access. The overall pattern, therefore, was that reconstructive recall discriminated all three diagnostic groups, while recollective recall discriminated healthy subjects from MCI subjects. For one, this suggests that some forms of memory decline are better markers of disease than others, and in this particular case, it suggests that declines in reconstructive recall are more closely connected to the HC → MCI → AD progression than recollective recall.

The idea that some forms of memory decline are better markers of unhealthy aging than others was also consistent with the analysis of longitudinal patterns of change in recall operations. Healthy subjects showed remarkably stable retrieval processes over time, as long as they remained healthy, a pattern that was very similar to what was found in the first study. However, MCI subjects showed steady declines in reconstruction over time, as long as they remained with MCI, and similarly, AD subjects showed steady declines in reconstruction and direct access over time, as long as they remained with AD. Such finding has at least two major implications. First, the longitudinal patterns indicate that over time, some retrieval processes decline faster than others during unhealthy aging. In MCI, longitudinal declines are primarily in the reconstruction domain, whereas in AD, longitudinal declines continue to occur

in the reconstruction domain but also occur in the recollective retrieval domain. Such a pattern has close resemblance to Dici et al.'s (2011) hypothesis about AD progression. According to their hypothesis, τ pathology in AD spreads from subhippocampal regions, which are related to "context-free" memories, towards the hippocampus, which is related to "context-rich" memories. If context-free memories provide a basis for reconstructive recall and direct access controls retrieval of context-rich memories, then their model of AD progression could explain the observed longitudinal patterns of change in reconstructive and recollective recall.

Second, the longitudinal patterns of change in retrieval processes are consistent with the idea that AD is a neurodegenerative disease, and more importantly, they inform about disease progression. As shown in Table 16, diagnostic group differences in reconstruction increase the longer subjects remain unhealthy. In MCI subjects, estimates of reconstruction after the first few study-test cycles of the RAVLT are particularly sensitive to MCI progression. In AD subjects, estimates of direct access and reconstruction on the first few study-test cycles of the RAVLT are particularly sensitive to AD progression. Notice that because many of the AD subjects in the ADNI were already AD patients when they were first enrolled in the study, it is likely that the longitudinal estimates of progression shown in Table 16 are actually being underestimated—if anything, such longitudinal trends are most likely higher than those shown in Table 16.

The overall pattern of changes in retrieval processes in healthy and unhealthy aging was fairly consistent with fuzzy-trace theory's prediction (Reyna & Mills, 2007). According to the theory's developmental principle, the ability to successfully

encode and retrieve verbatim traces of an event increases early in life, as the nervous system maturates, but decreases with advancing age, as the same system degenerates. The ability to encode and retrieve gist traces, on the other hand, is relatively more robust because the redundancy of their content (e.g., *rose*, *daisy*, *tulip*, *lotus*, and *dahlia* have an overlapping meaning, such as *type of flower*) decreases the chances that normal neural degeneration will greatly affect one's ability to recover the relational patterns preserved by gist traces. However, as the level of neural degeneration progresses from normal to abnormal, as in the transition from normal aging to MCI to AD, there should be greater impairment of gist memory. These two ideas, called the *neural integrity* and the *neural redundancy* hypotheses, were supported by findings reported in Reyna and Mills as well as the present studies. More specifically, normal aging decreased recollective recall and spared reconstructive recall, while AD and MCI decreased recollective recall even further but contrary to normal aging, unhealthy aging decreased reconstructive recall as well.

Lastly, it should be noted that in both studies, older subjects' age was always a reliable predictor of one or more retrieval process—always direct access though (see Tables 6 and 14). This is relevant because age is one of the main risk factors for AD—that is, older adults who are diagnosed as AD are usually older than MCI and healthy older adults. This is the main reason why in all analyses reported here, age was a covariate, because otherwise, it would confound the effects of diagnostic group. Similarly, the reported findings could not be explained by variability in depression because in both studies, when scores on the BDI were added to the multilevel model as covariate, the patterns of change in retrieval processes that were observed in healthy

and unhealthy aging remained the same. That is, the main effects and interactions reported in Tables 6 and 14 were still reliable when the model controlled for the number of depressive symptoms.

Conclusion

The developmental trajectories of three latent recall operations—direct access, reconstruction, and familiarity judgment—were investigated in samples of healthy subjects (younger and older adults) and unhealthy subjects (MCI and AD patients). The notion that normal age-related declines in episodic memory reflect changes in recollective retrieval (verbatim memory / recollection) was supported. In unhealthy aging, however, declines in reconstructive recall were the main marker of disease progression and the only operation able to differentiate healthy subjects from MCI subjects from AD subjects. Therefore, the reported findings suggest that healthy aging does not simply accelerate the normal aging process but instead, affect processes that are usually spared in healthy aging.

A logical next step for future work is to investigate the ability of the dual-retrieval model of recall to predict longitudinal transitions between diagnostic groups, and then compare its predictive power to other markers of disease, such as the presence of the ε4 allele of the apolipoprotein-E gene (Brainerd et al., 2011) and levels of Aβ / τ proteins in the cerebrospinal fluid (Motter et al., 1995). Because these were the first studies to look at longitudinal patterns of changes in recall operations during healthy and unhealthy aging, the focus was on the description of such changes more than prediction. Brainerd et al. (2014), for example, used subjects' baseline recall data to assess the model's ability to predict longitudinal changes in diagnostic group (HC→

HC vs. HC→MCI, and MCI→ MCI vs. MCI→AD). However, their approach is unable to use longitudinal patterns of change in parameter estimates to predict diagnostic group transitions. The findings reported in this dissertation suggested that the dual-retrieval model is able to identify disease-specific signatures in the longitudinal data, which ought to improve the model's ability to predict transitions between healthy and unhealthy aging.

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FOOTNOTES

1. The large attrition rate between Wave A and B in the sample of younger adults reflects the fact that only a subsample of the younger adults were followed longitudinally. Preliminary analyses showed that all their measures were very stable, and therefore, the likelihood that additional data collection would change the conclusions about their longitudinal patterns was too small to justify further tests.

APPENDIX A

Dual-Retrieval Model

In a multi-trial experiment in which subjects receive 3 study-test trials of form $S_1T_1\,S_2T_2\,S_3T_3$, each target (studied item) generates one out of eight possible patterns of correct (C) and error (E) responses across tests, namely $C_1C_2C_3$, $C_1C_2E_3$, …, $E_1E_2E_3$. The six parameters presented in Table 1 can be estimated from the frequency of such error-success patterns by applying a dual-recall Markov chain that contains those parameters. The states of the model are *U* (an initial no-recall state), *P* (an intermediate partial-recall state), with a correct recall state P_C and an incorrect recall state P_E, and *L* (a terminal and absorbing criterion-recall state). The Markov process for these states consists of the following starting vector **W** and transition matrices $\mathbf{M_1}$ and $\mathbf{M_2}$:

$$\mathbf{W} = [\mathrm{L}(1), \mathrm{P_E}(1), \mathrm{P_C}(1), \mathrm{U}(1)] = [D_1, (1\text{-}D_1)R_1(1\text{-}J_1), (1\text{-}D_1)R_1J_1, (1\text{-}D_1)(1\text{-}R_1)], \quad \text{(A1)}$$

$$\mathbf{M_1} = \begin{array}{c|cccc} & \mathrm{L}(2) & \mathrm{P_E}(2) & \mathrm{P_C}(2) & \mathrm{U}(2) \\ \hline \mathrm{L}(1) & 1 & 0 & 0 & 0 \\ \mathrm{P_E}(1) & D_2 & (1\text{-}D_2)(1\text{-}J_2) & (1\text{-}D_2)J_2 & 0 \\ \mathrm{P_C}(1) & 0 & (1\text{-}J_2) & J_2 & 0 \\ \mathrm{U}(1) & D_2 & (1\text{-}D_2)R_2(1\text{-}J_2) & (1\text{-}D_2)R_2J_2 & (1\text{-}D_2)(1\text{-}R_2) \end{array}, \quad \text{(A2)}$$

$$\mathbf{M_2} = \begin{array}{c|cccc} & L(3) & P_E(3) & P_C(3) & U(3) \\ \hline L(2) & 1 & 0 & 0 & 0 \\ P_E(2) & D_2 & (1-D_2)(1-J_2) & (1-D_2)J_2 & 0 \\ P_C(2) & 0 & (1-J_2) & J_2 & 0 \\ U(2) & D_2 & (1-D_2)R_2(1-J_2) & (1-D_2)R_2J_2 & (1-D_2)(1-R_2) \end{array} \quad \text{. (A3)}$$

The probabilities of the 8 individual error-success patterns are obtained by multiplying the starting vector and transition matrices together. Those expressions are:

$$P(C_1C_2C_3) = D_1 + (1-D_1)RJ_1J_2J_3; \quad \text{(A4)}$$

$$P(C_1C_2E_3) = (1-D_1)RJ_1J_2(1-J_3); \quad \text{(A5)}$$

$$P(C_1E_2C_3) = (1-D_1)RJ_1(1-J_2)D_2 + (1-D_1)RJ_1(1-J_2)(1-D_2)J_3; \quad \text{(A6)}$$

$$P(C_1E_2E_3) = (1-D_1)RJ_1(1-J_2)(1-D_2)(1-J_3)\ ; \quad \text{(A7)}$$

$$P(E_1C_2C_3) = (1-D_1)R(1-J_1)D_2 + (1-D_1)R(1-J_1)(1-D_2)J_2J_3 + (1-D_1)(1-R)D_2 + (1-D_1)(1-R)(1-D_2)RJ_2J_3; \quad \text{(A8)}$$

$$P(E_1C_2E_3) = (1-D_1)R(1-J_1)(1-D_2)J_2(1-J_3) + (1-D_1)(1-R)(1-D_2)RJ_2(1-J_3); \quad \text{(A9)}$$

$$P(E_1E_2C_3) = (1-D_1)R(1-J_1)(1-D_2)(1-J_2)D_2 + (1-D_1)R(1-J_1)(1-D_2)(1-J_2)(1-D_2)J_3 + (1-D_1)(1-R)(1-D_2)R(1-J_2)D_2 + (1-D_1)(1-R)(1-D_2)R(1-J_2)(1-D_2)J_3 + (1-D_1)(1-R)(1-D_2)(1-R)D_2 + (1-D_1)(1-R)(1-D_2)(1-R)(1-D_2)RJ_3; \quad \text{(A10)}$$

$$P(E_1E_2E_3) = (1-D_1)R(1-J_1)(1-D_2)(1-J_2)(1-D_2)(1-J_3) + (1-D_1)(1-R)(1-D_2)R(1-J_2)(1-D_2)(1-J_3) + (1-D_1)(1-R)(1-D_2)(1-R)(1-D_2)R(1-J_3) + (1-D_1)(1-R)(1-D_2)(1-R)(1-D_2)(1-R). \quad \text{(A11)}$$

Maximum likelihood estimates of the 6 parameters in Table 1 are then obtained by maximizing the following likelihood function using any optimization procedure:

$$L_6 = \Pi(p_i)^{N(i)}, \quad \text{(A12)}$$

in which the p_i are the 8 expressions on the right sides of Equations A4–A11, and the $N(i)$ are empirical data counts of the corresponding error-success sequences. Because 6 free parameters are estimated, the likelihood value in A12 is computed with 1 degree of freedom. A goodness-of-fit test that evaluates the null hypothesis that learning to recall involves two processes is then obtained by computing a likelihood ratio statistic that compares the likelihood in A12 to the likelihood of the same data when all 7 observable probabilities are free to vary. That test statistic, which is asymptotically distributed as $\chi^2(1)$, is

$$G^2 = -2\ln[L_6 / L_7], \quad \text{(A13)}$$

where L_7 is the likelihood of the data when all 7 observable probabilities are free to vary.

APPENDIX B

Associative Recall - Test Materials

Gender _____ **Subject #** _____

Age _____ **Date** _____

Experimenter _____

Instructions to Experimenter: **After filling the above information, please read the "Instructions for the Memory Test" to the subject. After that, proceed with the sequence of study and test trials for the list of 30 word pairs. Remember that on the study trials, you should read each pair of words to the subject as they appear on the screen. Remember that for each item on the test trials, you should simply: (1) circle the second word in each pair if the subject gives the correct response to the cue word; (2) do not do anything if the subject gives no response; (3) and if the subject gives a wrong word, print that word beside the correct response.**

Responses to Memory Tests – LIST 1

Subject # _____

Test 1a	**Test 1b**	**Test 2**	**Test 3**
1. Coke – Pencil	1. Woman – River	1. Coke – Pencil	1. Pigeon – Cucumber
2. Red – Saxophone	2. Coke – Pencil	2. Whale – Volcano	2. Star – Pet
3. Star – Pet	3. Caterpillar – Candle	3. Raincoats – Horse	3. Beetle – Diapers
4. Sink – Meat	4. Neck – Owl	4. Web – Kiss	4. Tape – Mink
5. Tape – Mink	5. Money – Uncle	5. Cookie – Mirror	5. Whale – Volcano
6. Eagle – Typewriter	6. Grapefruit – Test tube	6. Diamond – Olive	6. Girl – Building
7. Girl – Building	7. Web – Kiss	7. Ear – China	7. Surf – Hammer
8. Web – Kiss	8. Cottage – Skunk	8. Neck – Owl	8. Mouse – Weed
9. Neck – Owl	9. Blossom – Pillow	9. Mouse – Weed	9. Cookie – Mirror
10. Ear – China	10. Mouse – Weed	10. Money – Uncle	10. Grapefruit – Test tube
11. Money – Uncle	11. Cookie – Mirror	11. Eagle – Typewriter	11. Eagle – Typewriter
12. Cathedral – Onion	12. Pigeon – Cucumber	12. Surf – Hammer	12. Snow – Moose
13. Cookie – Mirror	13. Ear – China	13. Beaver – Lawn	13. Red – Saxophone
14. Blossom – Pillow	14. Diamond – Olive	14. Ski – Marijuana	14. Web – Kiss
15. Whale – Volcano	15. Student – Shirt	15. Cathedral – Onion	15. Cottage – Skunk
16. Yellow – Bath	16. Star – Pet	16. Blossom – Pillow	16. Student – Shirt
17. Student – Shirt	17. Red – Saxophone	17. Woman – River	17. Cathedral – Onion
18. Grapefruit – Test tube	18. Girl – Building	18. Cottage – Skunk	18. Coke – Pencil
19. Woman – River	19. Eagle – Typewriter	19. Red – Saxophone	19. Caterpillar – Candle
20. Mouse – Weed	20. Sink – Meat	20. Yellow – Bath	20. Money – Uncle
21. Raincoats – Horse	21. Cathedral – Onion	21. Tape – Mink	21. Yellow – Bath
22. Cottage – Skunk	22. Tape – Mink	22. Beetle – Diapers	22. Beaver – Lawn
23. Snow – Moose	23. Whale – Volcano	23. Sink – Meat	23. Ski – Marijuana
24. Surf – Hammer	24. Snow – Moose	24. Pigeon – Cucumber	24. Sink – Meat
25. Beaver – Lawn	25. Ski – Marijuana	25. Grapefruit – Test tube	25. Neck – Owl
26. Caterpillar – Candle	26. Raincoats – Horse	26. Student – Shirt	26. Raincoats – Horse
27. Ski – Marijuana	27. Beetle – Diapers	27. Star – Pet	27. Woman – River
28. Pigeon – Cucumber	28. Surf – Hammer	28. Girl – Building	28. Ear – China
29. Diamond – Olive	29. Beaver – Lawn	29. Snow – Moose	29. Blossom – Pillow
30. Beetle – Diapers	30. Yellow – Bath	30. Caterpillar – Candle	30. Diamond – Olive

Responses to Memory Tests – LIST 2

Subject # _____

Test 1a	**Test 1b**	**Test 2**	**Test 3**
1. Pimple – Hawk	1. Fog – Highway	1. Crayons - Sardine	1. Lemonade – Clover
2. Fog – Highway	2. Pajama – Jewel	2. Bluejay – Sunset	2. Mouth – Shower
3. Knight – Tooth	3. Squirrel – Child	3. Squirrel – Child	3. Diving – Cow
4. Mouth – Shower	4. Chestnut – Apartment	4. Fog - Highway	4. Bourbon – Cage
5. Bluejay – Sunset	5. Lamb – Artist	5. Heart – Battle	5. Chili – Blonde
6. Vegetable – Hockey	6. Skin – Father	6. Lunch – Wallet	6. Ocean – Jello
7. Dollar – Boy	7. Lunch – Wallet	7. Frog – Toilet	7. Mother – Cocktail
8. Orchestra – Train	8. Mother – Cocktail	8. Pajama – Jewel	8. Bluejay – Sunset
9. Diving – Cow	9. Bee – Chalk	9. Whiskey – Rose	9. Lunch – Wallet
10. Chestnut – Apartment	10. Bluejay – Sunset	10. Lettuce – Piano	10. Pimple – Hawk
11. Tiger – Tobacco	11. Lemonade – Clover	11. Chili – Blonde	11. Lamb – Artist
12. Whiskey – Rose	12. Chili – Blonde	12. Tiger – Tobacco	12. Bee – Chalk
13. Lunch– Wallet	13. Tiger – Tobacco	13. Pimple – Hawk	13. Tiger – Tobacco
14. Lips – Limousine	14. Mouth – Shower	14. Orchestra – Train	14. Squirrel – Child
15. Bourbon – Cage	15. Dollar – Boy	15. Lips – Limousine	15. Whiskey – Rose
16. Ocean – Jello	16. Vegetable – Hockey	16. Mother – Cocktail	16. Heart – Battle
17. Door – Banana	17. Hand – Bible	17. Chestnut – Apartment	17. Vegetable – Hockey
18. Bee – Chalk	18. Heart – Battle	18. Bourbon – Cage	18. Dollar – Boy
19. Skin – Father	19. Lips – Limousine	19. Bee – Chalk	19. Frog – Toilet
20. Squirrel – Child	20. Frog – Toilet	20. Lemonade – Clover	20. Pajama – Jewel
21. Lettuce – Piano	21. Crayons – Sardine	21. Diving – Cow	21. Orchestra – Train
22. Crayons – Sardine	22. Door – Banana	22. Vegetable – Hockey	22. Crayons – Sardine
23. Heart – Battle	23. Orchestra – Train	23. Ocean – Jello	23. Chestnut – Apartment
24. Pajama – Jewel	24. Ocean – Jello	24. Hand – Bible	24. Lettuce – Piano
25. Frog – Toilet	25. Whiskey – Rose	25. Skin – Father	25. Knight – Tooth
26. Hand – Bible	26. Pimple – Hawk	26. Mouth – Shower	26. Hand – Bible
27. Mother – Cocktail	27. Bourbon – Cage	27. Lamb – Artist	27. Door – Banana
28. Lamb – Artist	28. Lettuce – Piano	28. Dollar – Boy	28. Fog – Highway
29. Lemonade – Clover	29. Knight – Tooth	29. Door – Banana	29. Lips – Limousine
30. Chili – Blonde	30. Diving – Cow	30. Knight – Tooth	30. Skin – Father

Responses to Memory Tests – LIST 3

Subject # _____

Test 1a	**Test 1b**	**Test 2**	**Test 3**
1. Lemon – Stove	1. Lizard – Robin	1. Cars - Steak	1. Nun – Tomato
2. Gun – Boat	2. Jeep – Tulip	2. Trouser – Ferry	2. Prince – Milk
3. Men – Wine	3. Roof – Sailboat	3. Macaroni – Pants	3. Tongue – Glove
4. Roof – Sailboat	4. Cars – Steak	4. Flag – Mustard	4. Lizard – Robin
5. Lizard – Robin	5. Hurricane – Black	5. Iris – Emerald	5. Macaroni – Pants
6. Jeep – Tulip	6. Sofa – Trash	6. Jeep – Tulip	6. Blouse – Honey
7. Boulder – Clams	7. Teeth – Drum	7. Crown – Foot	7. Hospital – Rocket
8. Cars – Steak	8. Iris – Emerald	8. Nun – Tomato	8. Hurricane – Black
9. Flag – Mustard	9. Boulder – Clams	9. Sofa – Trash	9. Helmet – Potato
10. Forest – Male	10. Lemon – Stove	10. Lizard – Robin	10. Boulder – Clams
11. Hurricane – Black	11. Men – Wine	11. Tennis – Chair	11. Forest – Male
12. Baseball– Cat	12. Macaroni – Pants	12. Lemon – Stove	12. Men – Wine
13. Helmet – Potato	13. Gun – Boat	13. Roof – Sailboat	13. Ice cream – Glasses
14. Sofa – Trash	14. Crown – Foot	14. Ice cream – Glasses	14. Crown – Foot
15. Iris – Emerald	15. Baseball– Cat	15. Hurricane – Black	15. Cork – Pine
16. Cork – Pine	16. Flag – Mustard	16. Prince – Milk	16. Lemon – Stove
17. Crown – Foot	17. Helmet – Potato	17. Tree – Rope	17. Cars – Steak
18. Trouser – Ferry	18. Ice cream – Glasses	18. Boulder – Clams	18. Church – Morgue
19. Tennis – Chair	19. Cork – Pine	19. Baseball – Cat	19. Gun – Boat
20. Ice cream – glasses	20. Prince – Milk	20. Hospital – Rocket	20. Flag – Mustard
21. Clarinet – Shark	21. Forest – Male	21. Forest – Male	21. Trouser – Ferry
22. Prince – Milk	22. Clarinet – Shark	22. Church – Morgue	22. Sofa – Trash
23. Church – Morgue	23. Trouser – Ferry	23. Men – Wine	23. Iris – Emerald
24. Blouse– Honey	24. Tennis – Chair	24. Blouse – Honey	24. Tennis – Chair
25. Nun– Tomato	25. Tree – Rope	25. Teeth – Drum	25. Tree – Rope
26. Tongue – Glove	26. Church – Morgue	26. Cork – Pine	26. Roof – Sailboat
27. Teeth – Drum	27. Hospital – Rocket	27. Gun – Boat	27. Clarinet –Shark
28. Tree – Rope	28. Blouse– Honey	28. Helmet – Potato	28. Jeep – Tulip
29. Macaroni – Pants	29. Nun– Tomato	29. Clarinet – Shark	29. Teeth – Drum
30. Hospital – Rocket	30. Tongue – Glove	30. Tongue – Glove	30. Baseball – Cat

Responses to Memory Tests – LIST 4

Subject # _____

Test 1a	Test 1b	Test 2	Test 3
1. Beard – Trout	1. Jellyfish – Scissors	1. Window – Lake	1. Shoe – Body
2. Window – Lake	2. Shoe – Body	2. Bolt – Mule	2. Sword – Chicken
3. Alligator – Submarine	3. Sheep – Pie	3. Alligator – Submarine	3. Fishing – Knife
4. Plum – Smack	4. Sword – Chicken	4. Mountain – Head	4. Mountain – Head
5. Hotel – Sand	5. Tea – Eye	5. Wolf – Strawberry	5. Plum – Smack
6. Bed – Bell	6. Alligator– Submarine	6. Bread – Queen	6. Bed – Bell
7. Carnation – Kite	7. Spice – Rattlesnake	7. Flower – Bird	7. Wolf – Strawberry
8. Fishing – Knife	8. Beard – Trout	8. Beard – Trout	8. Alligator – Submarine
9. Soup – Wreck	9. Wolf – Strawberry	9. Grasshopper – Sister	9. Sandal – Volleyball
10. Wolf – Strawberry	10. Satin – Mattress	10. Hands – Sky	10. Carnation – Kite
11. Sandal – Volleyball	11. Lobster – Deer	11. Sheep – Pie	11. Soup – Wreck
12. Lobster – Deer	12. Broom – Propeller	12. Plum – Smack	12. Grasshopper – Sister
13. Hands – Sky	13. Bolt – Mule	13. Spice – Rattlesnake	13. Spice – Rattlesnake
14. Apple – Garbage	14. Fingers – Palace	14. Sandal – Volleyball	14. Tea – Eye
15. Mountain – Head	15. Burro – Grave	15. Sword – Chicken	15. Jellyfish – Scissors
16. Bread – Queen	16. Flower – Bird	16. Soup – Wreck	16. Bolt – Mule
17. Spice – Rattlesnake	17. Hotel – Sand	17. Broom – Propeller	17. Burro – Grave
18. Triangle – Water	18. Mountain – Head	18. Fingers – Palace	18. Hands – Sky
19. Sheep – Pie	19. Sandal – Volleyball	19. Carnation – Kite	19. Hotel – Sand
20. Fingers – Palace	20. Bread – Queen	20. Hotel – Sand	20. Triangle – Water
21. Burro – Grave	21. Window – Lake	21. Triangle – Water	21. Bread – Queen
22. Flower – Bird	22. Soup – Wreck	22. Satin – Mattress	22. Broom – Propeller
23. Tea – Eye	23. Carnation – Kite	23. Lobster – Deer	23. Lobster – Deer
24. Shoe – Body	24. Grasshopper – Sister	24. Tea – Eye	24. Satin – Mattress
25. Satin – Mattress	25. Hands – Sky	25. Apple – Garbage	25. Sheep – Pie
26. Grasshopper – Sister	26. Bed – Bell	26. Shoe – Body	26. Beard – Trout
27. Jellyfish – Scissors	27. Plum – Smack	27. Jellyfish – Scissors	27. Apple – Garbage
28. Sword – Chicken	28. Apple – Garbage	28. Fishing – Knife	28. Fingers – Palace
29. Broom – Propeller	29. Fishing – Knife	29. Bed – Bell	29. Flower – Bird
30. Bolt – Mule	30. Triangle – Water	30. Burro – Grave	30. Window – Lake

Responses to Memory Tests – LIST 5

Subject # _____

Test 1a	**Test 1b**	**Test 2**	**Test 3**
1. Skull – Heel	1. Leaf – Liver	1. Leaf – Liver	1. Toad – Cave
2. Garden– Cockpit	2. Orchid – Trumpet	2. Coffin – Spider	2. Coffin – Spider
3. Snake – Telephone	3. Feet - Beggar	3. Ball – Smile	3. Grape – Zoo
4. Swimming – Flood	4. Sleigh – Stew	4. Fire – City	4. Cigarette – Orange
5. Missile – Car	5. Shrimp – Soap	5. Missile – Car	5. Butterfly – Key
6. Beef – Rock	6. Photograph – Children	6. Beef – Rock	6. Orchid – Trumpet
7. Ape – Doughnut	7. Toad – Cave	7. Pickle – Zipper	7. Nose – Tomb
8. Butterfly – Key	8. Swimming – Flood	8. Butterfly – Key	8. Skull – Heel
9. Nose – Tomb	9. Nose – Tomb	9. Jacket – Raspberry	9. Ball – Smile
10. Shrimp – Soap	10. Jacket – Raspberry	10. Orchid – Trumpet	10. Lime – Cigar
11. Photograph – Children	11. Skull – Heel	11. Photograph – Children	11. Photograph – Children
12. Board – Circle	12. Chipmunk – Basketball	12. Garden – Cockpit	12. Necklace – Yacht
13. Lime– Cigar	13. Ball – Smile	13. Necklace – Yacht	13. Garden – Cockpit
14. Coffin – Spider	14. Plant – Kitten	14. Feet - Beggar	14. Chipmunk – Basketball
15. Orchid – Trumpet	15. Fruit – Dog	15. Lime – Cigar	15. Pickle – Zipper
16. Chipmunk – Basketball	16. Ape – Doughnut	16. Ape – Doughnut	16. Fruit – Dog
17. Feet – Beggar	17. Garden – Cockpit	17. Plant – Kitten	17. Beef – Rock
18. Sleigh – Stew	18. Missile – Car	18. Flea – Pup	18. Swimming – Flood
19. Flea – Pup	19. Flea – Pup	19. Swimming – Flood	19. Missile – Car
20. Toad – Cave	20. Fire – City	20. Board – Circle	20. Jacket – Raspberry
21. Leaf – Liver	21. Grape – Zoo	21. Sleigh – Stew	21. Plant – Kitten
22. Necklace – Yacht	22. Pickle – Zipper	22. Toad – Cave	22. Snake – Telephone
23. Pickle – Zipper	23. Board – Circle	23. Fruit – Dog	23. Ape – Doughnut
24. Plant – Kitten	24. Necklace – Yacht	24. Snake – Telephone	24. Board – Circle
25. Fire – City	25. Beef – Rock	25. Nose – Tomb	25. Flea – Pup
26. Jacket – Raspberry	26. Snake – Telephone	26. Grape – Zoo	26. Feet - Beggar
27. Ball – Smile	27. Lime – Cigar	27. Chipmunk – Basketball	27. Leaf – Liver
28. Grape – Zoo	28. Butterfly – Key	28. Shrimp – Soap	28. Fire – City
29. Fruit – Dog	29. Cigarette – Orange	29. Skull – Heel	29. Sleigh – Stew
30. Cigarette – Orange	30. Coffin – Spider	30. Cigarette – Orange	30. Shrimp – Soap

Responses to Memory Tests – LIST 6

Subject # _____

Test 1a	Test 1b	Test 2	Test 3
1. Pony – Cranberry	1. Doctor – Mosquito	1. Toe – Crocodile	1. Minister - Liquor
2. Minister – Liquor	2. Rain – Gorilla	2. Jockey – Bubble	2. Jockey - Bubble
3. Cloud – Café	3. Beach – Penny	3. Microscope – Dentist	3. Cake - Professor
4. Screwdriver – Leg	4. Bra – Canopener	4. Chocolate - Square	4. Rain - Gorilla
5. Vodka – Gym	5. Tangerine – Steam	5. Capsule – Oar	5. Flashbulbs - Bomb
6. Ant – Beer	6. Chocolate - Square	6. Bracelet – Needle	6. Capsule - Oar
7. Refrigerator- Lion	7. Cake - Professor	7. Dark – Rowboat	7. Fish - President
8. Tangerine - Steam	8. Bracelet – Needle	8. Refrigerator – Lion	8. Crabs - Box
9. Cradle – Smoke	9. Crabs – Box	9. Flashbulbs – Bomb	9. Cradle - Smoke
10. Nurse – Violin	10. Jockey – Bubble	10. Beach – Penny	10. Doctor - Mosquito
11. Chocolate- Square	11. Refrigerator- Lion	11. Ant – Beer	11. Jail - Telescope
12. Crabs – Box	12. Vodka – Gym	12. Tangerine – Steam	12. Chocolate - Square
13. Toe – Crocodile	13. Minister – Liquor	13. Spinach – Mansion	13. Beach - Penny
14. Coin – Duck	14. Cradle – Smoke	14. Doctor – Mosquito	14. Cloud – Café
15. Microscope – Dentist	15. Ant – Beer	15. Screwdriver – Leg	15. Fence – Sail
16. Jail – Telescope	16. Coin – Duck	16. Rain – Gorilla	16. Bracelet - Needle
17. Fence – Sail	17. Spinach – Mansion	17. University – Sun	17. Ant - Beer
18. Dark – Rowboat	18. Fence – Sail	18. Fence – Sail	18. Microscope - Dentist
19. Jockey – Bubble	19. Dark – Rowboat	19. Minister – Liquor	19. University - Sun
20. Capsule – Oar	20. Microscope – Dentist	20. Nurse – Violin	20. Toe - Crocodile
21. Spinach – Mansion	21. Flashbulbs – Bomb	21. Vodka – Gym	21. Coin - Duck
22. Fish – President	22. Pony – Cranberry	22. Cloud – Café	22. Pony - Cranberry
23. University – Sun	23. Capsule – Oar	23. Bra – Canopener	23. Screwdriver - Leg
24. Bra – Canopener	24. Jail – Telescope	24. Crabs – Box	24. Dark - Rowboat
25. Bracelet – Needle	25. Nurse – Violin	25. Cake – Professor	25. Refrigerator – Lion
26. Beach – Penny	26. Screwdriver – Leg	26. Jail – Telescope	26. Bra - Canopener
27. Flashbulbs – Bomb	27. Cloud – Café	27. Cradle – Smoke	27. Tangerine - Steam
28. Cake- Professor	28. Toe – Crocodile	28. Pony – Cranberry	28. Nurse - Violin
29. Doctor – Mosquito	29. University – Sun	29. Fish – President	29. Vodka - Gym
30. Rain – Gorilla	30. Fish – President	30. Coin – Duck	30. Spinach - Mansion

APPENDIX C

Beck Depression Inventory

Name_____ Marital Status:_____ Age:_____
Sex:_____
Occupation_____
Education:_____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike
0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness
0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying
0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't

11. Agitation
0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest
0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness
0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.
1 I sleep somewhat more *or* less than usual.
2 I sleep a lot more *or* less than usual.
3 I sleep most of the day *or* I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.
1 My appetite is somewhat more *or* less than usual.
2 My appetite is much less *or* greater than usual.
3 I have no appetite at all *or* I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

APPENDIX D

Demographic Questionnaire

Gender _____ Subject # _____
Age _____ Date _____
Experimenter_____

Are you of Hispanic, Latino, or Spanish origin?

□ No, not of Hispanic, Latino or Spanish origin
□ Yes, Mexican, Mexican American, Chicano
□ Yes, Puerto Rican
□ Yes, Cuban
□ Yes, Central American (fill in):_____
□ Yes, South American (fill in):_____
□ Yes, Spanish (Spain)

Select the one group that best describes you:

□ White
□ Black/ African American
□ Asian Indian □ Chinese □ Filipino □ Japanese □ Korean □ Vietnamese
□ Other Asian (fill in) : _____
□ Native American/ American Indian/ Alaskan Native (fill in Tribe):_____
□ Native Hawaiian or Other Pacific Islander
□ Mixed Ethnicity (example: Chicano and Native American):_____
□ Other (fill in):_____

How many years of schooling have you completed?

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Date of Birth:

Day_____Month_____ Year_____

Date of Session:

Day_____Month_____ Year_____

APPENDIX E
Shipley Vocabulary Inventory

SHIPLEY VOCABULARY INVENTORY

Gender _____ Subject # _____
Age _____ Date _____
Experimenter_____

VOCABULARY

In the test below, the first word in each line is printed in capital letters. Opposite are four other words. Draw a line under the one word which means the same thing, or most nearly the same thing, as the first word. A sample has been worked out for you. If you don't know, please guess. Be sure to underline the word in each line that means the same thing as the first word.

SAMPLE

LARGE	red	big	silent	wet

BEGIN HERE

1. **TALK**	draw	eat	speak	sleep
2. **PERMIT**	allow	sew	cut	drive
3. **PARDON**	forgive	pound	divide	tell
4. **COUCH**	pin	eraser	sofa	glass
5. **REMEMBER**	swim	recall	number	defy
6. **TUMBLE**	drink	dress	fall	think
7. **HIDEOUS**	silvery	tilted	young	dreadful
8. **CORDIAL**	swift	muddy	leafy	hearty
9. **EVIDENT**	green	obvious	skeptical	afraid
10. **IMPOSTER**	conductor	officer	book	pretender
11. **MERIT**	deserve	distrust	fight	separate
12. **FASCINATE**	welcome	fix	stir	enchant
13. **INDICATE**	defy	excite	signify	bicker
14. **IGNORANT**	red	sharp	uninformed	precise
15. **FORTIFY**	submerge	strengthen	vent	deaden
16. **RENOWN**	length	head	fame	loyalty
17. **NARRATE**	yield	buy	associate	tell
18. **MASSIVE**	bright	large	speedy	low
19. **HILARITY**	laughter	speed	grace	malice
20. **SMIRCHED**	stolen	pointed	remade	soiled
21. **SQUANDER**	tease	belittle	cut	waste
22. **CAPTION**	drum	ballast	heading	ape
23. **FACILITATE**	help	turn	strip	bewilder
24. **JOCOSE**	humorous	paltry	fervid	plain

25.	**APPRISE**	ereduce	stew	inform	delight
26.	**RUE**	eat	lament	dominate	cure
27.	**DENIZEN**	senator	inhabitant	fish	atom
28.	**DIVEST**	dispossess	intrude	rally	pledge
29.	**AMULET**	charm	orphan	dinge	pond
30.	**INEXORABLE**	untidy	involatile	rigid	sparse
31.	**SERRATED**	dried	notched	armed	blunt
32.	**LISSOME**	moldy	loose	supple	convex
33.	**MOLLIFY**	mitigate	direct	pertain	abuse
34.	**PLAGIARIZE**	appropriate	intend	revoke	maintain
35.	**ORIFICE**	brush	hole	building	lute
36.	**QUERULOUS**	maniacal	curious	devout	complaining
37.	**PARIAH**	outcast	priest	lentil	locker
38.	**ABET**	waken	ensue	incite	placate
39.	**TEMERITY**	rashness	timidity	desire	kindness
40.	**PRISTINE**	vain	sound	first	level

APPENDIX F

Health Questionnaire

Subject # _____
Date _____

How would you rate your health these past two months?

Excellent _____ Good _____ Fair _____ Poor_____

Have you had any of the following in the past six months?

Loss of consciousness for more than 5 minutes	Y	N
Alcohol or drug dependency	Y	N
Stroke	Y	N
Heart Attack	Y	N
Parkinson's Disease	Y	N
Current or recent chemotherapy	Y	N
Current use of psychotropic or antidepressant medications.	Y	N

APPENDIX G

Mini-Mental State Exam

Subject # _____
Date _____

The Examiner will ask the following questions. Write a 1 in the right column if the subject replies correctly or if the action the subject supplies is correct; Write a 0 in the right column if the answer or action is incorrect.

_____

The examiner will now say "Please answer the following questions."

What is the year?	
What is the season?	
What is the date?	
What is the day?	
What is the month?	
	TOTAL:

What state are we in?	
What county are we in?	
What town (or city) are we in?	
What is this building?	
What floor are we on?	
	TOTAL:

The examiner will now say "I'd like to test your memory. Please say these words: boat, cucumber, wire" (say all 3 words at once)

Boat	
Cucumber	
Wire	
	TOTAL:

The examiner will now say "Begin with 100 and count backwards by 7's

93	
86	
79	
72	
65	
	TOTAL:

The examiner will now say "Can you name the 3 objects I named before?"

Boat	
Cucumber	
Wire	
	TOTAL:

The examiner will now say “Name the following items” and point to a pencil, then a watch

Pencil	
Watch	
	TOTAL:

The examiner will now say “Repeat the following: No ifs, ands, or buts.”

Score a 1 if repeated correctly, 0 if said incorrectly	
	TOTAL:

The examiner will now say “Take a paper in your right hand, fold it in half, and put it on the floor.”

Takes the paper in their right hand	
Folds the paper in half	
Places the paper on the floor	
	TOTAL:

The examiner will now present a piece of paper that reads “CLOSE YOUR EYES” and then say “Read and obey the following”

Subject closes their eyes	
	TOTAL:

The examiner will now say “Write a sentence”

Subject writes a sentence	
	TOTAL:

The examiner draws interlocking pentagons and has the subject copy it

Patient copies the image	
	TOTAL:

TOTAL FOR ALL SECTIONS _____/30

APPENDIX H

Prospective-Retrospective Memory Questionnaire

Subject #_____
Date _____

Please use the following scale to answer the questions below:

1	2	3	4	5
Never	Rarely	Sometimes	Quite Often	Very Often

1. Do you decide to do something in a few minutes' time and then forget to do it?
_____

2. Do you fail to recognize a place you have visited before?
_____

3. Do you fail to do something you were supposed to do a few minutes later even though it's there in front of you, like take a pill or turn off the kettle?
_____

4. Do you forget something that you were told a few minutes before?
_____

5. Do you forget appointments if you are not prompted by someone else or by a reminder such as a calendar or diary?
_____

6. Do you fail to recognize a character in a radio or television show from scene to scene?
_____

7. Do you forget to buy something you planned to buy, like a birthday card, even when you see the shop?
_____

8. Do you fail to recall things that have happened to you in the last few days?
_____

9. Do you repeat the same story to the same person on different occasions?
_____

10. Do you intend to take something with you, before leaving a room or going out, but minutes later leave it behind, even though it's there in front of you?
_____

11. Do you mislay something that you have just put down, like a magazine or glasses?

_____

12. Do you fail to mention or give something to a visitor that you were asked to pass on?
_____

13. Do you look at something without realizing you have seen it moments before?
_____

14. If you tried to contact a friend or relative who was out, would you forget to try again later?
_____

15. Do you forget what you watched on television the previous day?
_____

16. Do you forget to tell someone something you had meant to mention a few minutes ago?
_____

Table 1

Parameters of the Dual-Recall Model

Parameter	State	Definition
		Recollective retrieval
Direct access		
D_1	L	The probability that an item's verbatim trace can be accessed after the first study trial.
D_2	L	The probability that an item's verbatim trace can be accessed following the first test if it could not be directly accessed on prior tests
		Nonrecollective retrieval
Reconstruction		
R_1	P	The probability that an item can be reconstructed from partially identifying information on the first test if it cannot be directly accessed
R_2	P	The probability that an item can be reconstructed from partially identifying information following the first test if it can neither be directly accessed nor reconstructed on prior tests

Familiarity judgment		
J_1	P_C	The probability that a reconstructed item is judged familiar to be output on the first test
J_2	P_C	The probability that a reconstructed item is judged familiar to be output following the first test

Table 2

Additional demographic variables for each age group in Waves A, B, and C

	Wave A		Wave B		Wave C	
Demographic variables	Older adults	Younger adults	Older adults	Younger adults	Older adults	Younger adults
Marital status						
Widowed	28.2%	0%	25.1%	0%	25.2%	0%
Divorced/Separated	11.8%	0%	10.2%	0%	9.2%	0%
Married	43.7%	0%	47.1%	0%	47.2%	0%
Single	16.4%	100%	17.6%	100%	18.4%	100%
Occupation						
Student	0.4%	100%	0%	100%	0%	100%
Other job	30.2%	0%	30.1%	0%	28.2%	0%
Retired	69.4%	0%	69.9%	0%	71.8%	0%
Education						

None	1.2%	0%	1.5%	0%	1.2%	0%
High school	21.8%	99.4%	21.8%	98.2%	21.2%	97.1%
Bachelors	26.2%	0.6%	25.4%	1.8%	27.1%	2.9%
Masters	32.7%	0%	31.5%	0%	30%	0%
Doctorates	13.3%	0%	15.2%	0%	15.3%	0%
Associates	4.8%	0%	4.6%	0%	5.3%	0%
Ethnicity						
Caucasian	96.1%	64.0%	97.4%	72.0%	98.2%	69.0%
African American	0.9%	9.0%	0.5%	12.0%	0.6%	13.8%
Asian	2.2%	22.0%	1.6%	14.0%	0.6%	13.8%
Other	0.9%	5.0%	0.5%	2.0%	0.6%	3.4%

Table 3

Summary statistics of scores on the neuropsychological tests for each age group in Waves A, B, and C

	Wave A		Wave B		Wave C	
Neuropsych tests	Older adults	Younger adults*	Older adults	Younger adults**	Older adults	Younger adults***
BDI	7.01 (6.57)	6.87 (5.38)	NA	NA	NA	NA
SVT	35.36 (4.32)	31.91 (3.94)	NA	NA	NA	NA
MMSE	27.00 (2.44)	27.60 (2.28)	26.25 (2.92)	28.69 (1.61)	27.05 (2.62)	29.00 (1.63)
PRMQ						
Prospective	19.27 (4.76)	19.91 (5.54)	19.48 (4.71)	22.24 (4.53)	19.31 (4.52)	20.81 (4.09)
Retrospective	16.89 (4.28)	16.65 (4.85)	16.73 (4.35)	17.76 (3.68)	16.65 (4.32)	17.44 (4.18)
Total	36.09 (8.40)	36.57 (9.74)	35.95 (8.37)	40.00 (7.42)	35.80 (8.26)	38.25 (7.25)

Note. *SD* in parenthesis. NA = Not administered. * 45 subjects of this group received neuropsychological tests. ** 29 subjects of this group received neuropsychological tests. *** 16 subjects of this group received neuropsychological tests.

Table 4

Summary statistics of the answers on the health questionnaire for each age group in Waves A, B, and C

	Wave A		Wave B		Wave C	
Health questionnaire	Older adults	Younger adults *	Older adults	Younger adults **	Older adults	Younger adults ***
Health rating for the last 2 months						
Poor	2.8%	0.0%	1.8%	0.0%	2.0%	0.0%
Fair	18.5%	6.8%	13.8%	10.7%	12.2%	0.0%
Good	49.4%	50.0%	59.6%	42.9%	61.2%	62.5%
Excellent	29.3%	43.2%	24.8%	46.4%	24.5%	37.5%
Experienced the following in the past 6 months						
Loss of consciousness	1.0%	0.0%	2.0%	4.0%	1.0%	6.0%
Alcohol/drug abuse	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Stroke	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Heart attack	0.0%	0.0%	2.0%	0.0%	2.0%	0.0%

Parkinson's disease	2.0%	0.0%	4.0%	0.0%	3.0%	0.0%
Chemotherapy	2.0%	0.0%	2.0%	0.0%	2.0%	0.0%
Use of psychotropic or antidepressant	22.0%	5.0%	14.0%	14.0%	14.0%	13.0%

* 45 subjects of this group received neuropsychological tests. ** 29 subjects of this group received neuropsychological tests. *** 16 subjects of this group received neuropsychological tests.

Table 5

Mean correct recall as a function of test, age group, and testing wave

	Wave A		Wave B		Wave C	
Recall test	Younger adults	Older adults	Younger adults	Older adults	Younger adults	Older adults
			List 1			
$T_{1a/b}$	.46	.15	.51	.23	.57	.23
T_2	.80	.39	.84	.48	.89	.49
T_3	.93	.53	.94	.61	.96	.62
Overall	.73	.36	.76	.44	.81	.45
			List 2			
$T_{1a/b}$	.61	.21	.62	.25	.64	.27
T_2	.90	.45	.88	.51	.91	.52
T_3	.96	.58	.95	.64	.96	.65
Overall	.82	.41	.82	.47	.84	.48

Table 6

Maximum likelihood estimates of the multilevel linear model's parameters

		Dual-retrieval model					
MLM parameter	Correct recall	D_1	D_2	J_1	J_2	R_1	R_2
γ00, intercept	.776*	.376*	.518*	.592*	.462*	.606*	.443*
γ01, (age group)	-.335*	-.284*	-.240*	.190*	-.025	-.265*	.174*
γ02, (30 - MMSE)	-.014*	-.006	-.020*	-.003	-.003	-.011	-.016*
γ02, (old age baseline - 75)	-.009*	-.004*	-.009*	.001	-.001	-.005*	-.003
γ10, (time)	.012	.047*	-.007	-.018	-.013	.014	-.009
γ11, (time)*(age group)	.004	-.030	.048	.012	.019	.028	.011
γ13, (time)*(30 - MMSE)	.005	.002	-.001	.004	.000	-.008	.004
γ12, (time)*(old age baseline - 75)	-.002	-.001	.000	-.001	-.001	.000	-.001

Note. Time and age are in years. MLM = Multilevel linear model. MMSE = Mini-mental state exam. * Maximum likelihood estimate reliable at the .05 significance level

Table 7

Mean maximum likelihood estimates of direct access, familiarity judgment, and reconstruction as a function of wave and age groups.

	Wave A		Wave B		Wave C	
Parameter	Younger adults	Older adults	Younger adults	Older adults	Younger adults	Older adults
			List 1			
D_1	.32	.05	.37	.09	.41	.10
D_2	.54	.18	.53	.24	.57	.27
J_1	.65	.78	.60	.79	.53	.79
J_2	.45	.44	.45	.44	.45	.44
R_1	.53	.27	.57	.32	.66	.31
R_2	.48	.56	.50	.60	.31	.59
			List 2			
D_1	.43	.08	.47	.11	.48	.12

D_2	.50	.23	.52	.27	.51	.30
J_1	.52	.78	.65	.75	.53	.77
J_2	.48	.42	.43	.44	.46	.43
R_1	.69	.32	.56	.37	.68	.36
R_2	.39	.56	.51	.57	.41	.57

Table 8

Main inclusion/exclusion criteria for each diagnostic group

Diagnostic group	Criteria
HC	(a) MMSE scores between 24 and 30; (b) CDR of 0; (c) non-depressed; (d) non-MCI; (e) non-demented; (f) age similar to MCI and AD subjects .
MCI	(a) MMSE scores between 24-30; (b) a memory complaint; (c) objective memory loss measured by adjusted scores on the Wechsler Memory Scale – Logical Memory II; (d) CDR of .5; (e) no significant impairment in cognitive domains other than memory; (f) daily living activities are not impaired; and (g) no dementia.
AD	(a) MMSE scores between 20 and 26; (b) CDR of .5 or 1.0; and (c) subject meets NINCDS-ADRDA criteria for probable AD.

Note. CDR = Clinical dementia rating. NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association.

Table 9

ADNI sample size as a function of months

	Month					
Diagnostic group	BL	6	12	18	24	36
HC	206	204	197	10	191	169
MCI	364	325	269	212	169	123
AD	178	188	213	84	234	117

Note. BL = Baseline. HC = Healthy control. MCI = Mild cognitive impairment. AD = Alzheimer's disease.

Table 10

Summary statistics of additional demographic variables for each diagnostic group in the ADNI at baseline

Demographic variables	HC	MCI	AD
Years of education*	16.10 (2.92)	15.70 (2.96)	14.85 (3.09)
Marital status			
Married	69%	80%	80%
Widowed	17%	12%	11%
Divorced	8%	7%	5%
Never married	6%	1%	4%
Unknown	0%	0%	0%
Ethnicity			
Caucasian	92%	94%	94%
African American	7%	4%	4%
Asian	1%	2%	1%
Other	0%	0%	1%

Note. HC = Healthy control. MCI = Mild cognitive impairment. AD = Alzheimer's disease. **SD* in parenthesis.

Table 11

Mean and SD of scores on the MMSE as a function of diagnostic group and session

	HC		MCI		AD	
Session	Mean	*SD*	Mean	*SD*	Mean	*SD*
Baseline	29.13	.97	27.04	1.79	23.30	2.05
6 months	29.02	1.05	26.64	2.62	22.28	3.52
12 months	29.17	1.13	26.92	2.48	21.69	4.31
18 months	29.30	1.25	26.82	2.74	23.00	3.84
24 months	29.16	1.03	26.96	2.93	2.25	5.56
36 months	29.05	1.31	27.12	3.40	21.03	5.53

Note. HC = Healthy control. MCI = Mild cognitive impairment. AD = Alzheimer's disease.

Table 12

Simplified ADNI-1 study schedule

	Screening & Baseline			Month 6			Month 12			Month 18			Month 24			Month 36		
Procedure	HC	MCI	AD	HC	MCI	AD	HC	MCI	AD	HC	MCI	AD	HC	MCI	AD	HC	MCI	AD
Explain study	x	x	x	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Obtain consent	x	x	x	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Demographics	x	x	x	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Neuropsych battery	x	x	x	x	x	x	x	x	x	.	x	.	x	x	x	x	x	.
Diagnostic summary	x	x	x	x	x	x	x	x	x	.	x	.	x	x	x	x	x	.

Note. HC = Healthy control. MCI = Mild cognitive impairment. AD = Alzheimer's disease.

Table 13

Mean overall recall on the RAVLT as a function of sessions and diagnostic groups

Session	HC	MCI	AD
Baseline	.58	.41	.31
6 months	.55	.38	.27
12 months	.59	.41	.28
18 months	.59	.39	.29
24 months	.61	.42	.25
36 months	.55	.41	.25

Note. HC = Healthy control. MCI = Mild cognitive impairment. AD = Alzheimer's disease. RAVLT = Rey Auditory Verbal Learning Task

Table 14

Maximum likelihood estimates of the multilevel linear model's parameters

MLM parameter	Correct recall	Dual-retrieval model					
		D_1	D_2	J_1	J_2	R_1	R_2
γ00, intercept	.570*	.271*	.198*	.790*	.532*	.408*	.359*
γ01, (age HC)	-.002*	-.006*	-.003*	.002	.001	.000	.000
γ10, (time HC)	-.008	-.003	-.003	.003	-.002	.003	.010
γ20, (MCI)	-.162*	-.095*	-.118*	-.133*	-.073*	-.019	-.127*
γ30, (time MCI)	-.021*	-.003	-.005	-.007	.004	-.005	-.019*
γ40, (AD)	-.258*	-.137*	-.156*	-.216*	-.096*	-.050*	-.226*
γ50, (time AD)	-.042*	-.013*	-.010	.007	-.012	-.046*	-.002
γ11, (time HC)*(age HC)	.000	.002*	.001	-.001	-.002	-.001	-.001
γ21, (MCI)*(age MCI)	.000	.005*	.002	-.002	-.001	-.001	-.001
γ31, (time MCI)*(age MCI)	.001	.000	.001	.001	.000	.001	.001
γ41, (AD)*(age AD)	.002	.007*	.002	-.002	-.004	-.002	.000

γ51, (time AD)*(age AD)	.002*	.000	.001	.001	.002	.001	-.002

Note. Time and age are in years. MLM = Multilevel linear model. HC = Healthy control. MCI = Mild cognitive impairment. AD = Alzheimer's disease. * Maximum likelihood estimate reliable at the .05 significance level

Table 15

Mean maximum likelihood estimates of direct access, familiarity judgment, and reconstruction parameters as a function of diagnostic group and session

Session	D_1	D_2	J_1	J_2	R_1	R_2
			HC			
Baseline	.26	.20	.81	.55	.40	.36
6 months	.26	.17	.77	.52	.40	.37
12 months	.27	.20	.80	.53	.42	.38
18 months	.32	.12	.76	.56	.44	.37
24 months	.30	.23	.78	.52	.42	.37
36 months	.24	.16	.81	.53	.40	.40
			MCI			
Baseline	.18	.08	.67	.45	.39	.26
6 months	.17	.07	.64	.47	.37	.19
12 months	.18	.08	.65	.47	.40	.20

18 months	.17	.06	.63	.46	.39	.20
24 months	.20	.09	.63	.46	.39	.22
36 months	.18	.07	.69	.49	.35	.24
			AD			
Baseline	.13	.05	.56	.41	.37	.15
6 months	.12	.04	.55	.43	.34	.10
12 months	.13	.03	.58	.44	.33	.12
18 months	.13	.03	.64	.47	.30	.14
24 months	.13	.02	.59	.40	.28	.14
36 months	.10	.02	.57	.46	.31	.11

Note. HC = Healthy control. MCI = Mild cognitive impairment. AD = Alzheimer's disease.

Table 16

Predicted longitudinal changes in parameter estimates as a function of diagnostic group in the ADNI

	Years in the diagnostic group					
Diagnostic group	0	.5	1	1.5	2	3
			D_1			
HC	.27	.27	.27	.26	.26	.26
MCI	.18	.17	.17	.17	.17	.17
AD	**.14**	**.13**	**.12**	**.12**	**.11**	**.10**
			D_2			
HC	.20	.20	.19	.19	.19	.19
MCI	.08	.08	.08	.07	.07	.07
AD	.04	.04	.03	.03	.02	.01
			J_1			
HC	.79	.79	.79	.79	.80	.80

MCI	.66	.65	.65	.65	.64	.64
AD	.57	.58	.58	.59	.59	.60
			J_2			
HC	.53	.53	.53	.53	.53	.53
MCI	.46	.46	.47	.47	.47	.48
AD	.43	.43	.42	.42	.42	.41
			R_1			
HC	.41	.41	.41	.41	.41	.41
MCI	.39	.39	.38	.38	.38	.37
AD	**.36**	**.33**	**.31**	**.29**	**.27**	**.22**
			R_2			
HC	.36	.36	.37	.37	.38	.39
MCI	**.23**	**.22**	**.21**	**.20**	**.19**	**.18**
AD	.13	.13	.13	.13	.13	.12

Note. Subjects' age when they first received a diagnosis was held constant (75 years). Values in bold indicate reliable longitudinal changes. HC = Healthy control. MCI = Mild cognitive impairment. AD = Alzheimer's disease.

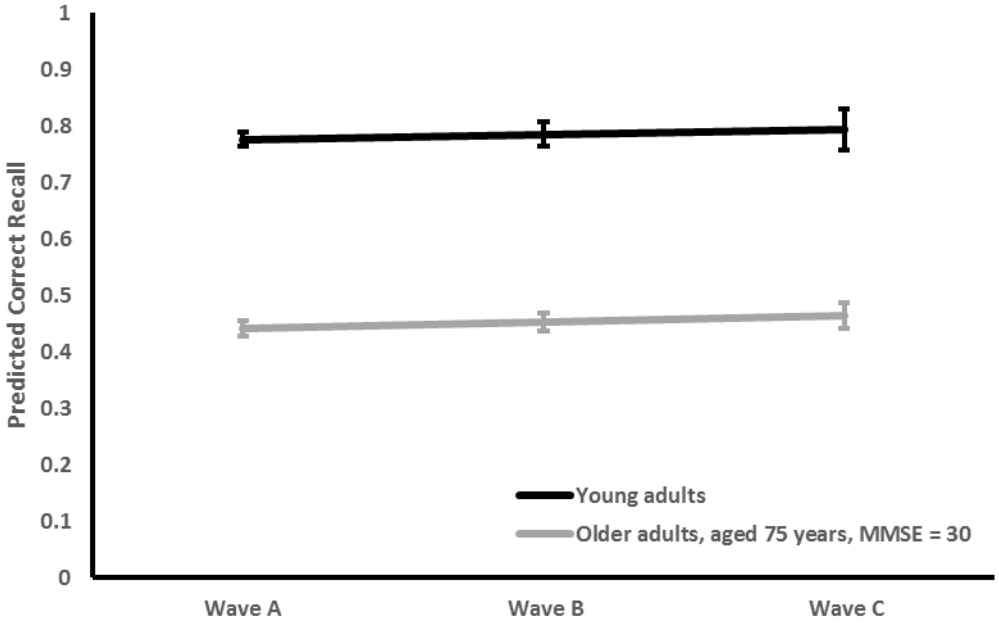

Figure 1. Predicted correct recall for younger and older adults as a function of Waves A, B, and C. Error bars are standard error.

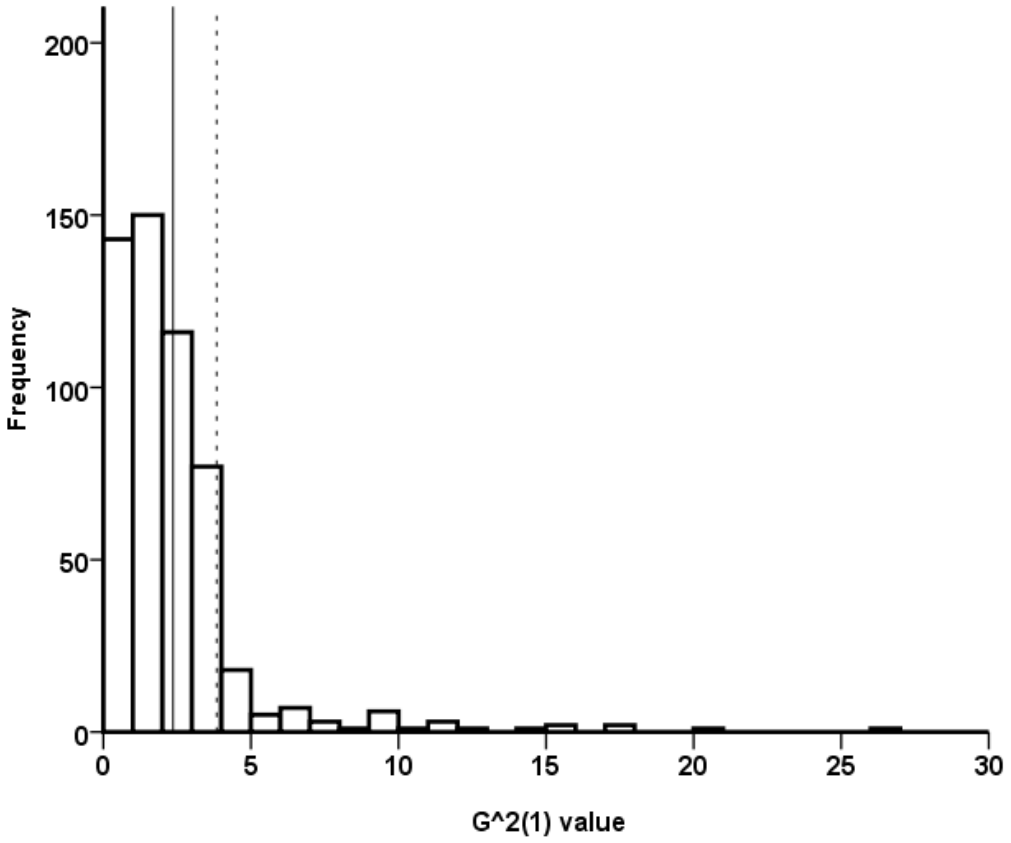

Figure 2. Distribution of the $G^2(1)$ statistic in the sample of younger adults. Dashed vertical line indicates the critical value to reject the null hypothesis of fit (3.84). Solid vertical line indicates the mean $G^2(1)$ value.

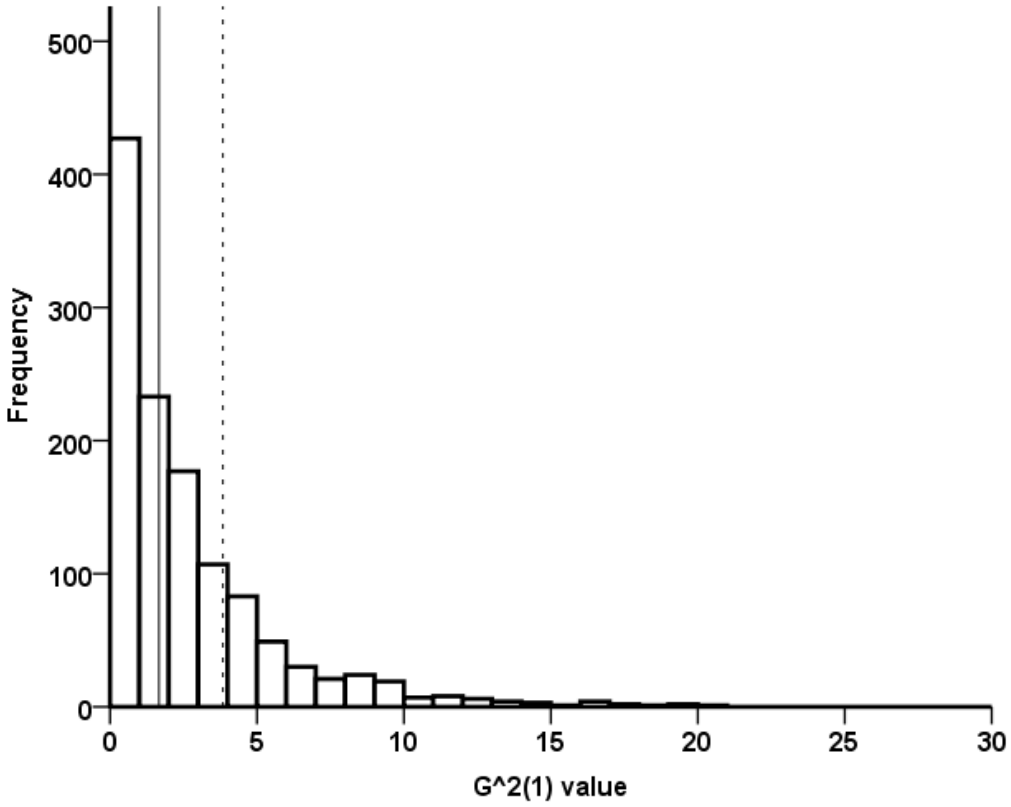

Figure 3. Distribution of the $G^2(1)$ statistic in the sample of older adults. Dashed vertical line indicates the critical value to reject the null hypothesis of fit (3.84). Solid vertical line indicates the mean $G^2(1)$ value.

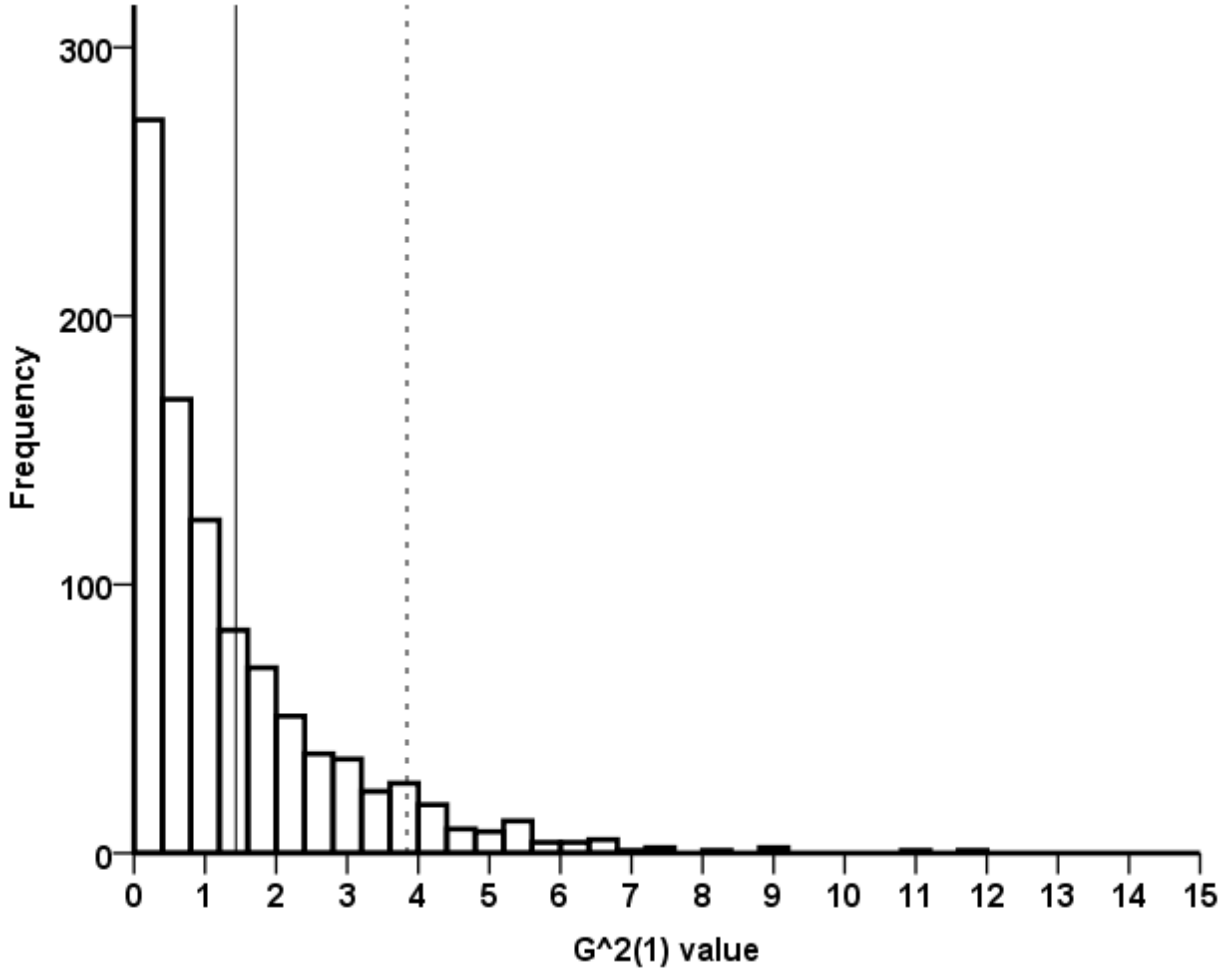

Figure 4. Distribution of the $G^2(1)$ statistic in the ADNI-1 sample of HC subjects. Dashed vertical line indicates the critical value to reject the null hypothesis of fit (3.84). Solid vertical line indicates the mean $G^2(1)$ value.

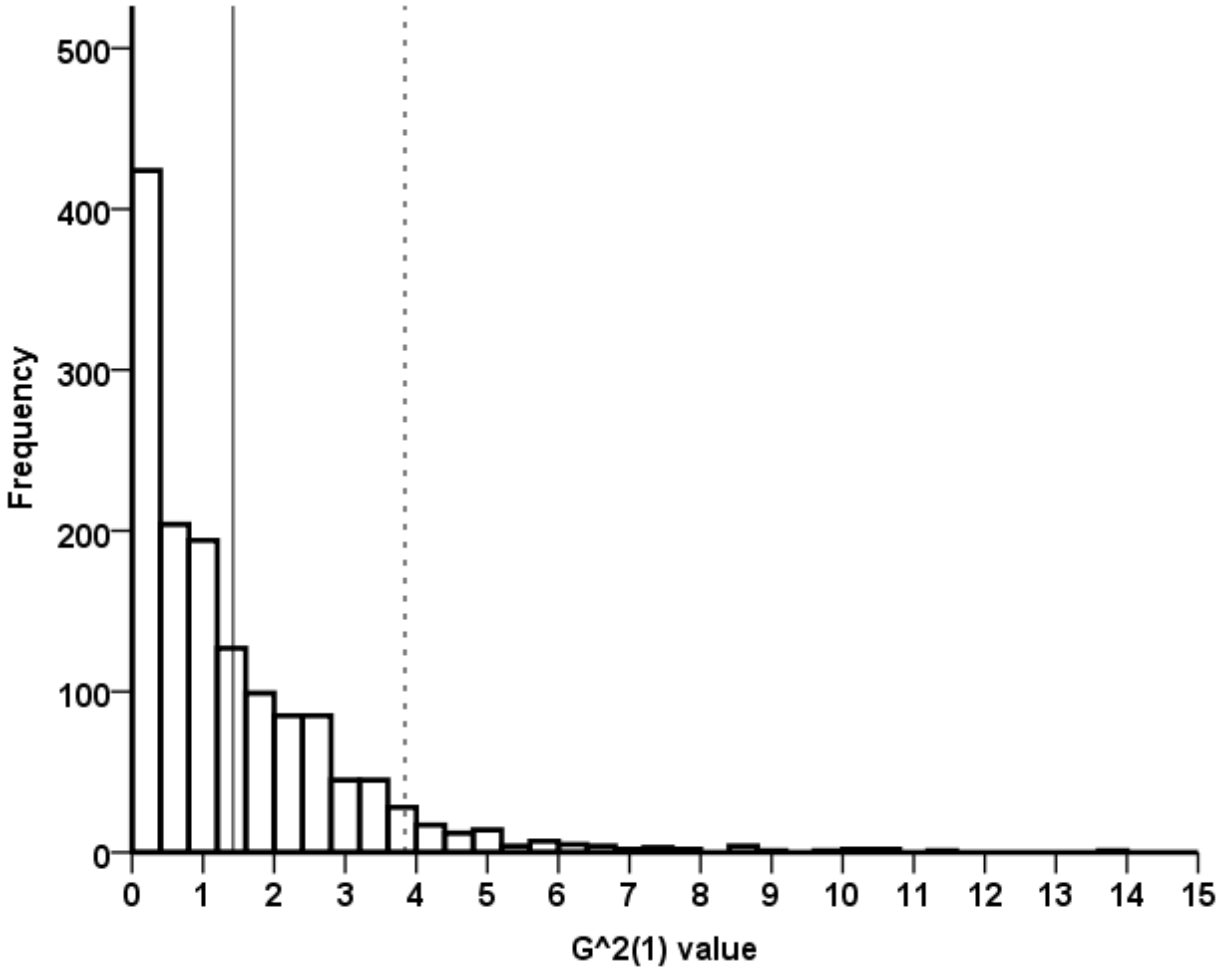

Figure 5. Distribution of the $G^2(1)$ statistic in the ADNI-1 sample of MCI subjects. Dashed vertical line indicates the critical value to reject the null hypothesis of fit (3.84). Solid vertical line indicates the mean $G^2(1)$ value.

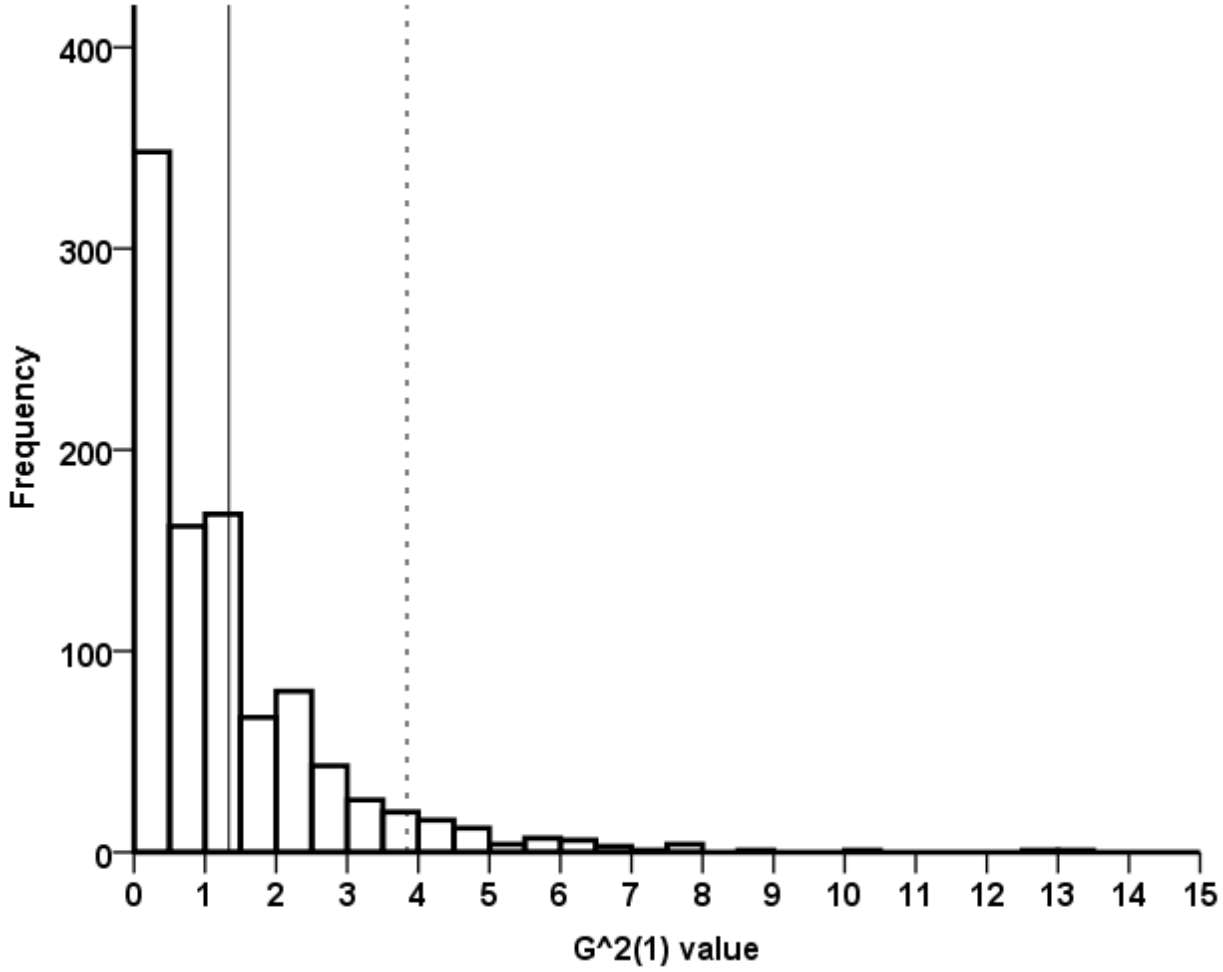

Figure 6. Distribution of the $G^2(1)$ statistic in the ADNI-1 sample of AD subjects. Dashed vertical line indicates the critical value to reject the null hypothesis of fit (3.84). Solid vertical line indicates the mean $G^2(1)$ value.